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(54) **Title:** HUMAN SECRETED PROTEINS

(57) **Abstract:** The present invention relates to human secreted polypeptides, and isolated nucleic acid molecules encoding said polypeptides, useful for diagnosing and treating gastrointestinal diseases, disorders, and/or conditions related thereto. Antibodies that bind these polypeptides are also encompassed by the present invention. Also encompassed by the invention are vectors, host cells, and recombinant and synthetic methods for producing said polynucleotides, polypeptides, and/or antibodies. The invention further encompasses screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further encompasses methods and compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Human Secreted Proteins

Field of the Invention

The present invention relates to human secreted proteins/polypeptides, and isolated nucleic acid molecules encoding said proteins/polypeptides, useful for detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal diseases and disorders. Antibodies that bind these polypeptides are also encompassed by the present invention. Also encompassed by the invention are vectors, host cells, and recombinant and synthetic methods for producing said polynucleotides, polypeptides, and/or antibodies. The invention further encompasses screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further encompasses methods and compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Background of the Invention

The human digestive system is a collection of specialized organs and body tissues that prepare food for use by hundreds of millions of body cells. Food when eaten cannot reach cells because it cannot pass through the intestinal walls to the bloodstream and, if it could would not be in a useful chemical state. The gastrointestinal system modifies food physically and chemically and disposes of unusable waste. Physical and chemical modification (digestion) depends on exocrine and endocrine secretions and controlled movement of food through the digestive tract.

The three fundamental processes of the digestive system are: secretion (e.g., delivery of enzymes, mucus, ions and the like into the lumen, and hormones into blood), absorption (e.g., transport of water, ions and nutrients from the lumen, across the epithelium and into blood), and motility (e.g., contractions of smooth muscle in the wall of the tube that crush, mix and propel its contents). Control of digestive function is achieved through a combination of electrical and hormonal messages which originate either within the digestive system's own nervous and endocrine systems, as well as from the central nervous system and from endocrine organs such as the adrenal gland.

The digestive system is composed of the digestive or alimentary tube and accessory digestive organs, which include the Mouth (e.g., tongue, taste buds, soft palate pharynx, salivary glands, teeth), Esophagus, Stomach, Liver, Gallbladder, Pancreas, Small Intestine (e.g., duodenum, jejunum, and ileum), and Large Intestine (e.g., caecum).

Common digestive system disorders including infections, inflammations, ulcers and cancers of the digestive or alimentary tube and above listed accessory digestive organs are described in more detail below.

Disorders of the Mouth

The mouth comprises an area from the lips to the front of the tonsils (fauces) at the start of the throat. The mouth contains the gums, teeth, and the tongue, together with salivary glands which secrete fluids that lubricate and begin food digestion as it is chewed. The roof of the mouth consists of the hard palate at the front and the soft palate at the back. The floor of the mouth comprises the tongue (controlled by a number of muscles attached to bones in the neck). At the front and sides of the tongue there are a number of taste buds. These respond to different tastes at different places (e.g., sweet, salty, sour, and bitter). At the back of the tongue there are some swellings which consist of lymphoid tissue. Underneath the tongue there is a midline attachment (frenulum) and the opening of several of the salivary ducts. There are other salivary glands (the parotid glands) lying over the angle of the jaw with a duct opening to the inside of the cheek at about the level of the second molar tooth.

Diseases and disorders of the mouth are vary greatly in manifested symptoms, frequencies, severities, and causes. Accordingly, diseases and disorders of the mouth may be caused or initiated by viruses, bacteria, genetics (e.g. autoimmune disorders), physical or chemical trauma, etc. For example, diseases and disorders of the mouth include canker sores (aphthous ulcers), herpetic stomatitis leukoplakia, gingivostomatitis, oral cancer, oral lichen lanus, oral thrush, histoplasmosis, salivary gland infections, glossitis, Hand, Foot and Mouth disease, salivary duct stones, mumps, etc.

Disorders of the Esophagus

Disorders of the Esophagus include dysphagia (e.g., difficulty in swallowing) and odynophagia (e.g., difficulty in swallowing accompanied by pain). Inflammatory disorders of the esophagus result from a variety of causes; for example, ingestion of noxious materials (e.g., corrosive esophagitis), lodgment of foreign bodies, or a complex of events associated with reflux of gastric contents from the stomach into the lower esophagus (e.g., peptic esophagitis).

Disorders of the motility of the esophagus tend to be either precipitated or aggravated at times of nervous stress. A disorder commonly due to obesity is gastric reflux. Persisting reflux of gastric contents with acid and digesting enzymes leads to chemical inflammation of the lining of the esophagus and ultimately to (peptic) ulceration. If inadequately treated, the process leads to submucosal fibrosis and stricturing, and, besides the symptoms of heartburn and regurgitation, the patient experiences pain on eating and swallowing.

Further disorders of the esophagus include the formation of diverticula. A serious injury to the esophagus is spontaneous rupture. It can occur in patients who have been vomiting or retching and in debilitated elderly persons with chronic lung disease. A rupture of this type confined to the mucosa only at the junction of the linings of the esophagus and stomach is called a Mallory-Weiss lesion.

Benign tumors of the esophagus originate in the submucosal tissues and principally are leiomyomas (tumors composed of smooth muscle tissue) or lipomas (tumors composed of adipose, or fat, tissues). Malignant tumors are either epidermal cancers, made up of unorganized aggregates of cells, or adenocarcinomas, in which there are gland-like formations. Cancers arising from squamous tissues are found at all levels of the organ, whereas adenocarcinomas are more common at the lower end where a number of glands of gastric origin are normally present. The prognosis is poor because diagnosis is difficult and the tumor has usually been growing for one or two years before symptoms are apparent.

Disorders of the stomach

Any disorder that affects the power of coordination of the stomach muscles is capable of producing symptoms ranging from those that are mildly unpleasant (e.g., anorexia and nausea) to others that are life-threatening. The intrinsic muscles of the stomach are innervated by branches of the vagus nerves, which travel along the esophagus from their point of emergence in the brain stem. Severing these nerves or altering their function by the use of anticholinergic medication may produce temporary or more prolonged change in the ability of the stomach to empty itself. Gastric retention may result from the degeneration of the nerves to the stomach that can result from diabetes mellitus. Obstruction due to scarring in the area of the gastric outlet, or to tumors encroaching on the lumen, causes the stomach to fill up with its own secretions as well as with partially digested food. In these circumstances, vomiting leads to dehydration and to electrolyte losses, which threaten life if not corrected.

Disorders of the stomach include ulcerative diseases, which involve mucosal breakdown either confined to the superficial layers of the mucosa (e.g., an erosion) or extending through the intrinsic layer of muscle of the mucosa into the tissues below (e.g., an ulcer). The circumstances that contribute to mucosal injury and ulcer formation include physical and chemical trauma that result from hot fluids and food, aspirin and other drugs, irritating spices, and pickling fluids. In addition, genetic factors are involved in the development of ulcers. The complications of peptic ulcers are hemorrhage, perforation, and obstruction of the outlet of the stomach (pyloric stenosis) by scarring of the duodenal bulb or of the pyloric channel. A diffuse inflammation of the stomach lining, gastritis, is usually an acute process caused by contaminated food, alcohol abuse, or by bacterial- or viral-induced inflammation of the gastrointestinal tract (gastroenteritis). The other form of gastritis is gastric atrophy, in which the thickness of the mucosa is diminished. Diffuse

gastric atrophy leads to partial loss of the glands and secreting cells throughout the stomach and may be associated with iron-deficiency anemia.

Malignant tumors of the stomach are common and are probably a result of both genetic and environmental factors. Gastric cancer affects men more often than women and accounts for about 20 percent of all deaths from cancers of the gastrointestinal tract in the United States. Other malignant tumors that involve the stomach are tumors ordinarily made up of lymphoid and connective tissue. Benign tumors, especially leiomyomas, are common and may, when large, cause massive hemorrhage. Polyps of the stomach are not common except in the presence of gastric atrophy.

Disorders of the Duodenum and Small Intestine

Primary cancer of the duodenum is an infrequent disease, however, benign tumors of the duodenum, particularly polyps and carcinoids, are more frequent. Cancers of the common bile duct or of the pancreas are important causes of death. A common disorder of the small intestine, distension, is caused by lack of coordination of the inner circular and outer longitudinal muscular layers of the intestinal wall which usually results in an accumulation of excess contents in the lumen. The most common cause of disturbed motility in the small intestine is food that contains an unsuitable additive, organism, or component. One of the most serious problems in small intestine are motor disturbances which arise from an intestinal obstruction that results from an actual encroachment on the bowel by an adhesive band or from an internal block produced by a tumor or gallstone. In addition, as profound an obstruction results when a portion of the intestine undergoes partial necrosis, or death, from failure of its blood supply.

The extremely common disorder known as the irritable bowel syndrome is probably due to a disturbance of the motility of the whole intestinal tract. The symptoms vary from watery diarrhea to constipation and the passage of stools with difficulty. When the colon is involved, an excess of mucus is often observed in the stools. Occasionally the irritable bowel syndrome may be due to an allergy to a particular foodstuff. The syndrome may develop following an infection such as bacillary dysentery, after which the small intestine remains irritable for many months.

A further disorder, malabsorption occurs when the small intestine is unable to transport properly broken down products of digestive materials from the lumen of the intestine into the lymphatics or mesenteric veins, where they are distributed to the rest of the body. Defects in transport occur either because the absorptive cells of the intestine lack certain enzymes, whether by birth defect or by acquired disease, or because they are hindered in their work by other disease processes that infiltrate the tissues, disturb motility, permit bacteria to overpopulate the bowel, or block the pathways over which transport normally proceeds. A malabsorption disorder of unknown cause, tropical sprue, is associated with partial atrophy of the mucosa of the small intestine. Disorders of the small intestine also include bacterial and parasitic infections.

Appendicitis is an inflammation of the vermiform appendix that may be caused by infection or partial or total obstruction. Chronic inflammations of the small intestine include tuberculosis and regional enteritis (Crohn's disease). Celiac disease causes damage to the mucosa of the small intestine, though it is not clear whether it is caused by an immune reaction, or an inability to break down a toxic protein, gluten, to smaller peptide fractions. Studies of the immune function of those with celiac disease suggest that at least a major part of the process is a delayed hypersensitivity reaction and that the morphological changes are correlated with the presence of circulating antibodies to gluten. The mucosal reaction results in progressive atrophy, with dwarfing, if not complete disappearance, of the microvilli and villi that line the intestinal tract.

Disorders of the Large Intestine

A wide variety of diseases and disorders occur in the large intestine. A disease that is analogous to achalasia of the esophagus is an idiopathic condition called aganglionic megacolon, or Hirschsprung's disease. It is characterized by the absence of ganglion cells and normal nerve fibres from the distal (or lower) portion of the large intestine, which results in reduced neuromuscular transmission and ceased peristalsis. The entire colon slowly becomes more and more distended and thick-walled. Abscesses in the perianal area are common complicating features of many diseases and disorders of the large intestine. Fungal and bacterial infections are also common causes of large intestine disorders.

The most common form of chronic colitis, ulcerative colitis, is idiopathic. It varies from a mild inflammation of the mucosa of the rectum, giving rise to excessive mucus and some spotting of blood in the stools, to a severe, sudden, intense illness, with destruction of a large part of the colonic mucosa, considerable blood loss, toxemia and, less commonly, perforation. The most common variety affects only the rectum and sigmoid colon and is characterized by diarrhea and the passage of mucus. Apart from the greater tendency for fistulas to form and for the wall of the intestine to thicken until the channel is obstructed, Crohn's disease is distinguishable from ulcerative colitis by microscopic findings. In Crohn's disease, the maximum damage occurs beneath the mucosa, and lymphoid conglomerations, known as granulomata, are formed in the submucosa. Crohn's disease attacks the perianal tissues more often than does ulcerative colitis. Although these two diseases are not common, they are disabling.

Tumors of the colon are usually polyps or cancers. A peculiar form of polyp is the villous adenoma, often a slowly growing, fernlike structure that spreads along the surface of the colon for some distance. Cancers compress the colonic lumen to produce obstruction, they attach to neighbouring structures to produce pain, and they perforate to give rise to peritonitis. Cancers also may metastasize to distant organs before local symptoms appear.

Anorectal disorders related to defecation are more common in the Western world than elsewhere. These disorders usually take the form of fissures (cuts or cracks in the skin or mucous

membrane) at the junction of the anal mucous membrane with the skin between the thighs. Anal fistulas sometimes occur as complications of serious bowel disease, as in tuberculosis or Crohn's disease of the bowel, or in certain parasitic diseases. A more general disorder is the enlargement of veins of the rectum and anus to form external or internal hemorrhoids. Hemorrhoids protrude, are associated with anal itching and pain, and bleed, especially when they come in contact with hard stools.

Disorders of the Liver

A variety of agents, including viruses, drugs, environmental pollutants, genetic disorders, and systemic diseases, can affect the liver. The resulting disorders usually affect one of the three functional components of the liver: the hepatocyte (liver cell) itself, the bile secretory (cholangiolar) apparatus, or the blood vascular system. Most acute liver diseases are self-limited, and liver functioning returns to normal once the causes are removed or eliminated. In some cases, however, the acute disease process destroys massive areas of liver tissue in a short time, leading to extensive death (necrosis) of hepatic cells and often to death of the patient. Hepatitis may result from viral infections or toxic damage from drugs or poisons. When acute hepatitis lasts for six months or more, a slow but progressive destruction of the surrounding liver cells and bile ducts occurs, a stage called chronic active hepatitis. If hepatocellular damage is severe enough to destroy entire acini (clusters of lobules), they are often replaced with fibrous scar tissue. Bile canaliculi and hepatocytes regenerate in an irregular fashion adjacent to the scar tissue and result in a chronic condition called cirrhosis of the liver. Where inflammatory activity continues after the onset of cirrhosis, the disorderly regeneration of hepatocytes and cholangioles may lead to the development of hepatocellular or cholangiolar cancer.

Although a number of viruses affect the liver, including the cytomegalovirus of infancy and childhood and the Epstein-Barr virus of infectious mononucleosis, there are three distinctive transmissible viruses that are specifically known to cause acute damage to liver cells: hepatitis virus A (HAV), hepatitis virus B (HBV), and hepatitis virus non-A, non-B (NANB). The symptoms characteristic of the acute hepatitis caused by the HAV, HBV, and NANB viruses are essentially indistinguishable from one another.

Acute hepatitis also may be caused by the overconsumption of alcohol or other poisons, such as commercial solvents (e.g., carbon tetrachloride), acetaminophen, and certain fungi. Such agents are believed to cause hepatitis when the formation of their toxic intermediate metabolites in the liver cell (phase I reactions) is beyond the capacity of the hepatocyte to conjugate, or join them with another substance for detoxification (phase II reactions) and excretion. Acute canalicular (cholestatic) hepatitis is most commonly caused by certain drugs, such as chlorpromazine, that lead to idiosyncratic reactions or, at times, by hepatitis viruses. Acute congestive liver disease usually results from the sudden engorgement of the liver by fluids after congestive heart failure.

A prominent autoimmune liver disease is Wilson's disease, which is caused by abnormal deposits of large amounts of copper in the liver. Granulomatous hepatitis, a condition in which localized areas of inflammation (granulomas) appear in any portion of the liver lobule, is a type of inflammatory disorder associated with many systemic diseases, including tuberculosis, sarcoidosis, schistosomiasis, and certain drug reactions. Granulomatous hepatitis rarely leads to serious interference with hepatic function, although it is often chronic. The end result of many forms of chronic liver injury is cirrhosis, or scarring of liver tissue in reponse to previous acinar necrosis and irregular regeneration of liver nodules and bile ducts.

Primary biliary cirrhosis, a widespread, though uncommon, autoimmune inflammatory disease of bile ducts, is a disorder primarily affecting middle-aged and older women. Secondary biliary cirrhosis results from chronic obstruction or recurrent infection in the extrahepatic bile ducts caused by strictures, gallstones, or tumors. Infestation of the biliary tract with a liver fluke, *Clonorchis sinensis*, is a cause of secondary biliary cirrhosis in Asia.

Portal hypertension, the increased pressure in the portal vein and its tributaries that is the result of impediments to venous flow into the liver, is brought about by the scarring characteristic of the cirrhotic process. The increased pressure causes feeders of the portal vein to distend markedly, producing varices, or dilations of the veins. When varices are located in superficial tissues, they may rupture and bleed profusely. Two such locations are the lower esophagus and the perianal region. The accumulation of fluid in the abdominal cavity, or ascites, is related to portal hypertension, significant reduction in serum albumin, and renal retention of sodium. When albumin levels in blood are lower than normal, there is a marked reduction in the force that holds plasma water within the blood vessels and normally resists the effects of the intravascular pressure. The resulting increase in intravascular pressure, coupled with the increased internal pressure caused by the portal venous obstruction in the liver, leads to massive losses of plasma water into the abdominal cavity. The associated reduction of blood flow to the kidneys causes increased elaboration of the hormone aldosterone, which, in turn, causes the retention of sodium and water and a reduction in urinary output. In addition, because the movement of intestinal lymph into the liver is blocked by the cirrhotic process in the liver, the backflow of this fluid into the abdominal cavity is greatly increased. A progressive reduction in kidney function that often occurs in persons with advanced acute or chronic liver disease, hepatorenal syndrome, probably results from an inadequate perfusion of blood through the cortical (outer) portions of the kidneys, where most removal of waste products occurs. With advanced hepatocytic dysfunction, a spasm of blood vessels in the renal cortex can occur, often with good blood flow to the rest of the kidney. This spasm results in progressive failure in kidney function and often leads to death.

Although not uncommon, cancer originating in the liver, usually in hepatocytes and less frequently in cells of bile duct origin, is rare in the West and is almost always associated with active cirrhosis, particularly the form found in patients with chronic hepatitis. Long exposure to

certain environmental poisons, such as vinyl chloride or carbon tetrachloride, has also been shown to lead to hepatic cancer. Cancers arising elsewhere in the body, particularly in abdominal organs, lungs, and lymphoid tissue, commonly lead to metastatic cancer in the liver and are by far the most frequent type of hepatic malignancy. Various benign types of tumors and cysts arise from certain components of the liver, such as the hepatocytes (adenomas) or blood vessels (hemangiomas). While the cause of these lesions is not always clear, hepatic adenomas are associated with the prolonged use of female sex hormones (estrogens). Benign cysts in the liver may occur as congenital defects or as the result of infections from infestation of the dog tapeworm (*Echinococcus granulosus*). Abscesses on the liver result from the spread of infection from the biliary tract or from other parts of the body, especially the appendix and the pelvic organs. Specific liver abscesses also result from infections with the intestinal parasite *Entamoeba histolytica*.

Disorders of the Biliary Tract

Cholelithiasis, or the formation of gallstones in the gallbladder, is the most common disease of the biliary tract. There are three types of Gallstones: stones containing primarily calcium bilirubinate (pigment stones); stones containing 25 percent or more of cholesterol; and stones composed of variable mixtures of both bilirubin and cholesterol (mixed gallstones). Pigment stones are the result of an increased amount of bilirubin in the liver (due to hemolytic disease) and the consequent secretion into the biliary tract of increased amounts of the water-soluble conjugate, bilirubin diglucuronide, a pigment that is normally secreted in the urine. Cholesterol and mixed cholesterol-bilirubinate stones occur when the proportion of cholesterol in bile exceeds the capacity of bile acids and lecithin to contain the total amount of cholesterol in micellar colloidal solution. Postcholecystectomy syndrome comprises painful attacks, often resembling preoperative symptoms, that occasionally occur following the surgical removal of gallstones and the gallbladder. These attacks may be related to intermittent muscular spasms of the sphincter of Oddi or of the bile ducts.

Cancer of the biliary tract is rare but may occur in almost any area, including the gallbladder, the hepatic ducts, the common bile duct, or the ampulla of Vater. In cancer of the bile duct, congenital cysts and parasitic infections, such as liver flukes, seem to lead to increased risks. Persons with extensive chronic ulcerative colitis also show a greater than normal incidence of bile duct carcinoma.

Jaundice, or yellowing of the skin, scleras, and mucous membranes, occurs whenever the level of bilirubin in the blood is significantly above normal. This condition is evident in three different types of disorders including, unconjugated, or hemolytic, jaundice; hepatocellular jaundice; and cholestatic, or obstructive jaundice. Unconjugated jaundice results when the amount of bilirubin produced from hemoglobin by the destruction of red blood cells or muscle tissue (myoglobin) overwhelms the normal capacity of the liver to transport it or when the ability of the

liver to conjugate normal amounts of bilirubin into bilirubin diglucuronide is significantly reduced by inadequate intracellular transport or enzyme systems. Hepatocellular jaundice arises when liver cells are damaged so severely that their ability to transport bilirubin diglucuronide into the biliary system is reduced, allowing some of this yellow pigment to regurgitate into the bloodstream. Cholestatic jaundice, occurs when essentially normal liver cells are unable to transport bilirubin either through the hepatocytic-bile capillary membrane, because of damage in that area, or through the biliary tract, because of anatomical obstructions (e.g., atresias, gallstones, cancer).

Disorders of the Pancreas

Inflammation of the pancreas, or pancreatitis, is probably the most common disease of this organ. The disorder may be confined to either singular or repeated acute episodes, or it may become a chronic disease. There are many factors associated with the onset of pancreatitis, including direct injury, certain drugs, viral infections, heredity, hyperlipidemia (increased levels of blood fats), and congenital derangements of the ductal system. Localized, severe abdominal and midback pain resulting from enzyme leakage, tissue damage, and nerve irritation is the most common symptom of acute pancreatitis. In severe cases, respiratory failure, shock, and even death may occur. Chronic pancreatitis rarely follows repeated acute attacks. It seems instead to be a separate disorder that results in mucus plugs and precipitation of calcium salts in the smaller pancreatic ducts. Mucous production and plugging of the pancreas in Cystic fibrosis patients almost invariably causes destruction and scarring of the acinar tissue, usually without damaging the islets of Langerhans. A similar process in the hepatic biliary system produces foci of fibrosis and bile duct proliferation, a singular form of cirrhosis.

The discovery of new human digestive system associated polynucleotides, the polypeptides encoded by them, and antibodies that immunospecifically bind these polypeptides, satisfies a need in the art by providing new compositions which are useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diseases and disorders of the digestive system, including, but not limited to, dysphagia, odynophagia, congenital disorders of the esophagus, gastric reflux, diverticula, Mallory-Weiss lesions, leiomyomas of the esophagus, lipoma, anorexia, nausea, ulcerative disease, pyloric stenosis, gastroenteritis, gastritis, gastric atropy, gastric cancer, benign tumors of the duodenum (e.g., polyps and carcinoids), pancreatic cancer, cancer of the bile duct, distension, irritable bowel syndrome, malabsorption, congenital disorders of the small intestine (e.g., Meckel's diverticulum, multiple diverticula), bacterial and parasitic infection (e.g., traveler's diarrhea, typhoid, paratyphoid, cholera, roundworms, tapeworms, amoebae, hookworms, strongyloides, threadworms, and blood flukes), megacolon (e.g., Hirschsprung's disease, aganglionic megacolon, acquired megacolon), colitis (e.g., due to bacterial, fungal, or parasitic infection, ulcerative colitis), tumors of the colon (e.g., polyps or cancers), anorectal disorders (e.g., anal fistulas, hemorrhoids, hepatitis (e.g., acute, chronic,

persistent hepatitis, viral (for example, hepatitis caused by hepatitis virus A (HAV), hepatitis virus B (HBV), and hepatitis virus non-A, non-B (NANB) infection), congenital disorders of the liver (e.g., Wilson's disease, hemochromatosis, cystic fibrosis, biliary atresia, and alpha1-antitrypsin deficiency), cirrhosis, portal hypertension, cholelithiasis, cancer of the biliary tract, jaundice (e.g., unconjugated, hemolytic, hepatocellular, cholestatic, or obstructive jaundice).

The discovery of new human gastrointestinal-associated polynucleotides, the polypeptides encoded by them, and antibodies that immunospecifically bind these polypeptides, satisfies a need in the art by providing new compositions which are useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal-specific diseases and disorders described in more detail below.

Summary of the Invention

The present invention encompasses human secreted proteins/polypeptides, and isolated nucleic acid molecules encoding said proteins/polypeptides, useful for detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal diseases and disorders. Antibodies that bind these polypeptides are also encompassed by the present invention; as are vectors, host cells, and recombinant and synthetic methods for producing said polynucleotides, polypeptides, and/or antibodies. The invention further encompasses screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention also encompasses methods and compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Detailed Description

Polynucleotides and Polypeptides of the Invention

Description of Table 1A

Table 1A summarizes information concerning certain polypnucleotides and polypeptides of the invention. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID:", for a cDNA clone related to each contig sequence disclosed in Table 1A. Third column, the cDNA Clones identified in the second column were deposited as indicated in the third column (i.e. by ATCC Deposit No:Z and deposit date). Some of the deposits contain multiple different clones corresponding to the same gene. In the fourth column, "Vector" refers to the type of vector contained in the corresponding cDNA Clone identified in the second column. In the fifth column, the nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous

("overlapping") sequences obtained from the corresponding cDNA clone identified in the second column and, in some cases, from additional related cDNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X. In the sixth column, "Total NT Seq." refers to the total number of nucleotides in the contig sequence identified as SEQ ID NO:X." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." (seventh column) and the "3' NT of Clone Seq." (eighth column) of SEQ ID NO:X. In the ninth column, the nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly , in column ten, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep." In the eleventh column, the translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be routinely translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

In the twelfth and thirteenth columns of Table 1A, the first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." In the fourteenth column, the predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion". The amino acid position of SEQ ID NO:Y of the last amino acid encoded by the open reading frame is identified in the fifteenth column as "Last AA of ORF".

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table 1A and/or elsewhere herein

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA

sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1A. The nucleotide sequence of each deposited plasmid can readily be determined by sequencing the deposited plasmid in accordance with known methods

The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular plasmid can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

Also provided in Table 1A is the name of the vector which contains the cDNA plasmid. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res. 16:*7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res. 17:*9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies 5:*58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene

Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus 15:*59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res. 16:*9677-9686 (1988) and Mead, D. *et al., Bio/Technology 9:* (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or a deposited cDNA (cDNA Clone ID). The corresponding gene can be isolated in

accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X and SEQ ID NO:Y using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue. .

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X and/or a cDNA contained in ATCC Deposit No.Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by a cDNA contained in ATCC deposit No.Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X and/or a polypeptide encoded by the cDNA contained in ATCC Deposit No.Z, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the cDNA contained in ATCC Deposit No.Z.

Description of Table 1B (Comprised of Tables 1B.1 and 1B.2)

Table 1B.1 and Table 1B.2 summarize some of the polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID:), contig sequences (contig identifier (Contig ID:) and contig nucleotide sequence identifiers (SEQ ID NO:X)) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby. The first column of Tables 1B.1 and 1B.2 provide the gene numbers in the application for each clone identifier. The second column of Tables 1B.1 and 1B.2 provide unique clone identifiers, "Clone ID:", for cDNA clones related to each contig sequence disclosed in Table 1A and/or Table 1B. The third column of Tables 1B.1 and 1B.2 provide unique contig identifiers, "Contig ID:" for each of the contig sequences disclosed in these tables. The fourth column of Tables 1B.1 and 1B.2 provide the sequence identifiers, "SEQ ID NO:X", for each of the contig sequences disclosed in Table 1A and/or 1B.

Table 1B.1

The fifth column of Table 1B.1, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:X that delineates the preferred open reading frame (ORF) that encodes the amino acid sequence shown in the sequence listing and referenced in Table 1B.1 as SEQ ID NO:Y (column 6). Column 7 of Table 1B.1 lists residues comprising predicted epitopes contained in the polypeptides encoded by each of the preferred ORFs (SEQ ID NO:Y). Identification of potential immunogenic regions was performed according to the method of Jameson and Wolf (CABIOS, 4; 181-186 (1988)); specifically, the Genetics Computer Group (GCG) implementation of this algorithm, embodied in the program PEPTIDESTRUCTURE (Wisconsin Package v10.0, Genetics Computer Group (GCG), Madison, Wisc.). This method returns a measure of the probability that a given residue is found on the surface of the protein. Regions where the antigenic index score is greater than 0.9 over at least 6 amino acids are indicated in Table 1B.1 as "Predicted Epitopes". In particular embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the predicted epitopes described in Table 1B.1. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. Column 8 of Table 1B.1 ("Cytologic Band") provides the chromosomal location of polynucleotides corresponding to SEQ ID NO:X. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM™. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). If the putative chromosomal location of the Query overlaps with the chromosomal location of a Morbid Map entry, an OMIM identification number is disclosed in Table 1B.1, column 9 labeled "OMIM Disease Reference(s)". A key to the OMIM reference identification numbers is provided in Table 5.

Table 1B.2

Column 5 of Table 1B.2, "Tissue Distribution" shows the expression profile of tissue, cells, and/or cell line libraries which express the polynucleotides of the invention. The first code number shown in Table 1B.2 column 5 (preceding the colon), represents the tissue/cell source identifier code corresponding to the key provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. The second number in column 5 (following the colon), represents the number of times a sequence corresponding to the reference polynucleotide sequence (e.g., SEQ ID NO:X) was identified in the corresponding tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate

information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of ^{33}P dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression.

Description of Table 1C

Table 1C summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID:), contig sequences (contig identifier (Contig ID:) contig nucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier, "Clone ID:", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO:X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID:" for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO:A" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO:B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon From-To", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention that are also exemplary members of polynucleotide sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

Description of Table 1D

Table 1D: In preferred embodiments, the present invention encompasses a method of detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal

diseases or disorders; comprising administering to a patient in which such treatment, prevention, or amelioration is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) represented by Table 1A, Table 1B, and Table 1C, in an amount effective to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate the disease or disorder.

As indicated in Table 1D, the polynucleotides, polypeptides, agonists, or antagonists of the present invention (including antibodies) can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists thereof (including antibodies) could be used to treat the associated disease.

Table 1D provides information related to biological activities for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table 1D also provides information related to assays which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("cDNA Clone ID:") provides the unique clone identifier for each clone as previously described and indicated in Tables 1A, 1B, and 1C. The third column ("AA SEQ ID NO:Y") indicates the Sequence Listing SEQ ID Number for polypeptide sequences encoded by the corresponding cDNA clones (also as indicated in Tables 1A, 1B, and 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides (or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and provides information pertaining to the various types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity. Table 1D describes the use of FMAT technology, *inter alia*, for testing or demonstrating various biological activities. Fluorometric microvolume assay technology (FMAT) is a fluorescence-based system which provides a means to perform nonradioactive cell- and bead-based assays to detect activation of cell signal transduction pathways. This technology was designed specifically for ligand binding and immunological assays. Using this technology, fluorescent cells or beads at the bottom of the well are detected as localized areas of concentrated fluorescence using a data processing system. Unbound flurophore comprising the background signal is ignored, allowing for a wide variety of homogeneous assays. FMAT technology may be used for peptide ligand binding assays, immunofluorescence, apoptosis, cytotoxicity, and bead-based immunocapture assays. *See*, Miraglia S et. al., "Homogeneous cell and bead based assays for highthroughput screening using flourometric microvolume assay technology," Journal of Biomolecular Screening; 4:193-204 (1999). In particular, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides (including polypeptide fragments and variants) to activate signal transduction

pathways. For example, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides to upregulate production of immunomodulatory proteins (such as, for example, interleukins, GM-CSF, Rantes, and Tumor Necrosis factors, as well as other cellular regulators (e.g. insulin)).

Table 1D also describes the use of kinase assays for testing, demonstrating, or quantifying biological activity. In this regard, the phosphorylation and de-phosphorylation of specific amino acid residues (e.g. Tyrosine, Serine, Threonine) on cell-signal transduction proteins provides a fast, reversible means for activation and de-activation of cellular signal transduction pathways. Moreover, cell signal transduction via phosphorylation/de-phosphorylation is crucial to the regulation of a wide variety of cellular processes (e.g. proliferation, differentiation, migration, apoptosis, etc.). Accordingly, kinase assays provide a powerful tool useful for testing, confirming, and/or identifying polypeptides (including polypeptide fragments and variants) that mediate cell signal transduction events via protein phosphorylation. See e.g., Forrer, P., Tamaskovic R., and Jaussi, R. "Enzyme-Linked Immunosorbent Assay for Measurement of JNK, ERK, and p38 Kinase Activities" Biol. Chem. 379(8-9): 1101-1110 (1998).

Description of Table 2

Table 2 summarizes homology and features of some of the polypeptides of the invention. The first column provides a unique clone identifier, "Clone ID:", corresponding to a cDNA clone disclosed in Table 1A or Table 1B. The second column provides the unique contig identifier, "Contig ID:" corresponding to contigs in Table 1B and allowing for correlation with the information in Table 1B. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequence. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. Comparisons were made between polypeptides encoded by the polynucleotides of the invention and either a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM") as further described below. The fifth column provides a description of the PFAM/NR hit having a significant match to a polypeptide of the invention. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in columns five and six. Columns 8 and 9, "NT From" and "NT To" respectively, delineate the polynucleotides in "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth and sixth columns. In specific embodiments polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence encoded by a polynucleotide in SEQ ID NO:X as delineated in columns 8 and 9, or fragments or variants thereof.

Description of Table 3

Table 3 provides polynucleotide sequences that may be disclaimed according to certain embodiments of the invention. The first column provides a unique clone identifier, "Clone ID", for a cDNA clone related to contig sequences disclosed in Table 1B. The second column provides the sequence identifier, "SEQ ID NO:X", for contig sequences disclosed in Table 1A and/or Table 1B. The third column provides the unique contig identifier, "Contig ID:", for contigs disclosed in Table 1B. The fourth column provides a unique integer 'a' where 'a' is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, and the fifth column provides a unique integer 'b' where 'b' is any integer between 15 and the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. For each of the polynucleotides shown as SEQ ID NO:X, the uniquely defined integers can be substituted into the general formula of a-b, and used to describe polynucleotides which may be preferably excluded from the invention. In certain embodiments, preferably excluded from the invention are at least one, two, three, four, five, ten, or more of the polynucleotide sequence(s) having the accession number(s) disclosed in the sixth column of this Table (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone).

Description of Table 4

Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1B.2, column 5. Column 1 of Table 4 provides the tissue/cell source identifier code disclosed in Table 1B.2, Column 5. Columns 2-5 provide a description of the tissue or cell source. Note that "Description" and "Tissue" sources (i.e. columns 2 and 3) having the prefix "a_" indicates organs, tissues, or cells derived from "adult" sources. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease." The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

Description of Table 5

Table 5 provides a key to the OMIM reference identification numbers disclosed in Table

1B.1, column 9. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). Column 2 provides diseases associated with the cytologic band disclosed in Table 1B.1, column 8, as determined using the Morbid Map database.

Description of Table 6

Table 6 summarizes some of the ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application. These deposits were made in addition to those described in the Table 1A.

Description of Tablé 7

Table 7 shows the cDNA libraries sequenced, and ATCC designation numbers and vector information relating to these cDNA libraries.

The first column shows the first four letters indicating the Library from which each library clone was derived. The second column indicates the catalogued tissue description for the corresponding libraries. The third column indicates the vector containing the corresponding clones. The fourth column shows the ATCC deposit designation for each libray clone as indicated by the deposit information in Table 6.

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as

well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence encoding SEQ ID NO:Y or a fragment or variant thereof (e.g., the polypeptide delinated in columns fourteen and fifteen of Table 1A); a nucleic acid sequence contained in SEQ ID NO:X (as described in column 5 of Table 1A and/or column 3 of Table 1B) or the complement thereof; a cDNA sequence contained in Clone ID: (as described in column 2 of Table 1A and/or Table 1B and contained within a library deposited with the ATCC); a nucleotide sequence encoding the polypeptide encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 (EXON From-To) of Table 1C or a fragment or variant thereof; or a nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1C or the complement thereof. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown, for example, in column 2 of Table 1B, each clone is identified by a cDNA Clone ID (identifier generally referred to herein as Clone ID:). Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. Table 7 provides a list of the deposited cDNA libraries. One can use the Clone ID: to determine the library source by reference to Tables 6 and 7. Table 7 lists the deposited cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone (Clone ID) isolated from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1A and/or Table 1B correlates the Clone ID names with SEQ ID NO:X. Thus, starting with an SEQ ID NO:X, one can use Tables 1A, 1B, 6, 7, and 9 to determine the corresponding Clone ID, which library it came from and which ATCC deposit the library is contained in. Furthermore, it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the

Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), the polynucleotide sequence delineated in columns 7 and 8 of Table 1A or the complement thereof, the polynucleotide sequence delineated in columns 8 and 9 of Table 2 or the complement thereof, and/or cDNA sequences contained in Clone ID: (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments, or the cDNA clone within the pool of cDNA clones deposited with the ATCC, described herein), and/or the polynucleotide sequence delineated in column 6 of Table 1C or the complement thereof. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured

salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

"SEQ ID NO:X" refers to a polynucleotide sequence described in column 5 of Table 1A, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 10 of Table 1A. SEQ ID NO:X is identified by an integer specified in column 6 of Table 1A. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. The polynucleotide sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, a polypeptide sequence corresponding to polynucleotide sequence SEQ ID NO:2 is the first polypeptide sequence shown in the sequence listing. The

second polypeptide sequence corresponds to the polynucleotide sequence shown as SEQ ID NO:3, and so on.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

"SEQ ID NO:X" refers to a polynucleotide sequence described, for example, in Tables 1A, Table 1B, or Table 2, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 11 of Table 1A and or column 6 of Table 1B.1. SEQ ID NO:X is identified by an integer specified in column 4 of Table 1B. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. "Clone ID:" refers to a cDNA clone described in column 2 of Table 1A and/or 1B.

"A polypeptide having functional activity" refers to a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein. Such functional activities include, but are not limited to, biological activity (e.g. activity useful in

treating, preventing and/or ameliorating gastrointestinal diseases and disorders), antigenicity (ability to bind [or compete with a polypeptide for binding] to an anti-polypeptide antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

The polypeptides of the invention can be assayed for functional activity (e.g. biological activity) using or routinely modifying assays known in the art, as well as assays described herein. Specifically, one of skill in the art may routinely assay secreted polypeptides (including fragments and variants) of the invention for activity using assays as described in the examples section below.

"A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

TABLES:

Table 1A

Table 1A summarizes information concerning certain polypnucleotides and polypeptides of the invention. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID:", for a cDNA clone related to each contig sequence disclosed in Table 1A. Third column, the cDNA Clones identified in the second column were deposited as indicated in the third column (i.e. by ATCC Deposit No:Z and deposit date). Some of the deposits contain multiple different clones corresponding to the same gene. In the fourth column, "Vector" refers to the type of vector contained in the corresponding cDNA Clone identified in the second column. In the fifth column, the nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the corresponding cDNA clone identified in the second column and, in some cases, from additional related cDNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X. In the sixth column, "Total NT Seq." refers to the total number of nucleotides in the contig sequence identified as SEQ ID NO:X." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." (seventh

column) and the "3' NT of Clone Seq." (eighth column) of SEQ ID NO:X. In the ninth column, the nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, in column ten, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep." In the eleventh column, the translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be routinely translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

In the twelfth and thirteenth columns of Table 1A, the first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." In the fourteenth column, the predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion". The amino acid position of SEQ ID NO:Y of the last amino acid encoded by the open reading frame is identified in the fifteenth column as "Last AA of ORF".

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table 1A and/or elsewhere herein

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1A. The nucleotide sequence of each deposited

plasmid can readily be determined by sequencing the deposited plasmid in accordance with known methods

The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular plasmid can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

Also provided in Table 1A is the name of the vector which contains the cDNA plasmid. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res. 16:*7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res. 17:*9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies 5:*58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene

Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus 15:*59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res. 16:*9677-9686 (1988) and Mead, D. *et al., Bio/Technology 9:* (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or a deposited cDNA (cDNA Clone ID). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X and SEQ ID NO:Y using information from the sequences

disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X and/or a cDNA contained in ATCC Deposit No.Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by a cDNA contained in ATCC deposit No.Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X and/or a polypeptide encoded by the cDNA contained in ATCC Deposit No.Z, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the cDNA contained in ATCC Deposit No.Z.

Table 1A

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	H2CBU83	209889 05/22/98	pBluescript SK-	11	2703	1	2703	157	157	300	1	30	31	207
1	H2CBU83	209889 05/22/98	pBluescript SK-	189	2709	1	2709	157	157	478	1	30	31	51
2	H6EDC19	209324 10/02/97	Uni-ZAP XR	12	760	324	760	389	389	301	1	25	26	114
3	HACBD91	209626 02/12/98	Uni-ZAP XR	13	1445	1	1445	117	117	302	1	42	43	49
4	HAGAQ26	209368 10/16/97	Uni-ZAP XR	14	1333	157	1333	251	251	303	1	20	21	62
5	HAGDS35	209299 09/25/97	Uni-ZAP XR	15	751	1	751	45	45	304	1	23	24	122
5	HAGDS35	209299 09/25/97	Uni-ZAP XR	190	813	1	813	52	52	479	1	23	24	118
6	HAJAN23	PTA-322 07/09/99	pCMVSport 3.0	16	2849	1	2849	109	109	305	1	15	16	563
6	HAJAN23	PTA-322 07/09/99	pCMVSport 3.0	191	2288	1	2288	120	120	480	1	15	16	169
7	HAJBR69	209626 02/12/98	pCMVSport 3.0	17	755	1	755	262	262	306	1	19	20	53
8	HAMFE15	203364 10/19/98	pCMVSport 3.0	18	4129	1	4129	1495	1495	307	1	34	35	421

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
8	HAMFE15	203364 10/19/98	pCMVSport 3.0	192	3758	1	3758	226	226	481	1	23	24	47
9	HAMGR28	209965 06/11/98	pCMVSport 3.0	19	1674	47	1674	98	98	308	1	18	19	242
9	HAMGR28	209965 06/11/98	pCMVSport 3.0	193	1534	1	1534	40	40	482	1	18	19	203
10	HAPOM49	209878 05/18/98	Uni-ZAP XR	20	2005	1	2005	251	251	309	1	22	23	189
10	HAPOM49	209878 05/18/98	Uni-ZAP XR	194	2664	1	2664	448	448	483	1	1	2	123
11	HATBR65	209626 02/12/98	Uni-ZAP XR	21	812	1	812	252	252	310	1	16	17	64
12	HAUAI83	209626 02/12/98	Uni-ZAP XR	22	910	1	886	253	253	311	1	18	19	49
12	HAUAI83	209626 02/12/98	Uni-ZAP XR	195	1076	1	1076		575	484	1	10	11	23
13	HBAMB15	209683 03/20/98	pSport1	23	821	330	821	390	390	312	1	19	20	59
14	HBGBA69	209878 05/18/98	Uni-ZAP XR	24	981	1	981	124	124	313	1	38	39	240
14	HBGBA69	209878 05/18/98	Uni-ZAP XR	196	943	1	933	62	62	485	1	38	39	60
15	HBIAE26	209224 08/28/97	Uni-ZAP XR	25	1038	1	1038	75	75	314	1	18	19	39
16	HBINS58	PTA-885 10/28/99	pCMVSport 3.0	26	843	1	843	57	57	315	1	30	31	174

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstAA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
16	HBINS58	PTA-885 10/28/99	pCMVSport 3.0	197	1566	1	1566	71	71	486	1	29	30	173
16	HBINS58	PTA-885 10/28/99	pCMVSport 3.0	198	1067	1	1067	100	100	487	1	29	30	210
17	HBNAW17	209242 09/12/97	Uni-ZAP XR	27	601	1	601	77	77	316	1	37	38	61
18	HCE2F54	209626 02/12/98	Uni-ZAP XR	28	1276	19	1256	166	166	317	1	19	20	319
19	HCE3G69	209878 05/18/98	Uni-ZAP XR	29	2084	1	2084	165	165	318	1	19	20	336
19	HCE3G69	209878 05/18/98	Uni-ZAP XR	199	2078	1	2078	165	165	488	1	19	20	105
20	HCE5F43	209580 01/14/98	Uni-ZAP XR	30	1765	1	1765	113	113	319	1	20	21	272
21	HCEFB80	PTA-2069 06/09/00	Uni-ZAP XR	31	2494	1	2494	12	12	320	1	35	36	89
21	HCEFB80	PTA-2069 06/09/00	Uni-ZAP XR	200	2494	1	2451	5	5	489	1	35	36	89
22	HCEWE20	209300 09/25/97	Uni-ZAP XR	32	885	13	885	166	166	321	1	18	19	51
23	HCGMD59	209627 02/12/98	pCMVSport 2.0	33	790	1	780	438	438	322	1	30	31	74
24	HCNDR47	PTA-855 10/18/99	Lambda ZAP II	34	1343	1	1343	21	21	323	1	24	25	127
24	HCNDR47	PTA-855 10/18/99	Lambda ZAP II	201	845	1	845	124	124	490	1	47	48	127

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstA A of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
24	HCNDR47	PTA-855 10/18/99	Lambda ZAP II	202	738	1	738		603	491	1	8	9	9
25	HCNSM70	209580 01/14/98	pBluescript	35	1089	1	1089	107	107	324	1	26	27	215
25	HCNSM70	209580 01/14/98	pBluescript	203	1145	62	1145	161	161	492	1	26	27	91
26	HCUIM65	209324 10/02/97	ZAP Express	36	875	331	736	557	557	325	1	27	28	47
27	HCWDS72	209852 05/07/98	ZAP Express	37	320	1	320	19	19	326	1	17	18	100
28	HCWKC15	209324 10/02/97	ZAP Express	38	710	1	710	37	37	327	1	18	19	40
29	HDHEB60	209215 08/21/97	pCMVSport 2.0	39	1421	235	1421	568	568	328	1	24	25	108
30	HDPBA28	PTA-163 06/01/99	pCMVSport 3.0	40	3447	197	3447	259	259	329	1	32	33	941
30	HDPBA28	PTA-163 06/01/99	pCMVSport 3.0	204	4909	1	4909	69	69	493	1	32	33	941
31	HDPCL63	PTA-1544 03/21/00	pCMVSport 3.0	41	3037	115	3037	35	35	330	1	58	59	267
31	HDPCL63	PTA-1544 03/21/00	pCMVSport 3.0	205	2921	1	2921	260	260	494	1	17	18	157
31	HDPCL63	PTA-1544 03/21/00	pCMVSport 3.0	206	1259	358	1259		605	495	1	6	7	118
32	HDPCO25	209125 06/19/97	pCMVSport 3.0	42	767	76	767	182	182	331	1	20	21	53

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstA A of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
33	HDPFP29	209626 02/12/98	pCMVSport 3.0	43	1057	1	1057	293	293	332	1	30	31	52
34	HDPGT01	203027 06/26/98	pCMVSport 3.0	44	2687	138	2687	8	8	333	1	28	29	87
35	HDPHI51	209125 06/19/97	pCMVSport 3.0	45	728	1	728	245	245	334	1	30	31	40
36	HDPJM30	209563 12/18/97	pCMVSport 3.0	46	1635	308	1633	59	59	335	1	59	60	525
36	HDPJM30	209563 12/18/97	pCMVSport 3.0	207	1314	1	1313	259	259	496	1	20	21	59
37	HDPMM88	PTA-848 10/13/99	pCMVSport 3.0	47	4893	1	4893	100	100	336	1	37	38	937
37	HDPMM88	PTA-848 10/13/99	pCMVSport 3.0	208	468	1	468	141	141	497	1	20	21	109
37	HDPMM88	PTA-848 10/13/99	pCMVSport 3.0	209	181	1	181		44	498	1	7	8	46
37	HDPMM88	PTA-848 10/13/99	pCMVSport 3.0	210	612	1	612		419	499	1			6
37	HDPMM88	PTA-848 10/13/99	pCMVSport 3.0	211	1024	1	1024		111	500	1	5	6	11
37	HDPMM88	PTA-848 10/13/99	pCMVSport 3.0	212	366	18	321		167	501	1	1	2	56
37	HDPMM88	PTA-848 10/13/99	pCMVSport 3.0	213	519	1	519		28	502	1	1	2	53
38	HDPOJ08	209878 05/18/98	pCMVSport 3.0	48	1655	1	1655	159	159	337	1	18	19	122

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
39	HDPPN86	PTA-867 10/26/99	pCMVSport 3.0	49	6297	1	6297	127	127	338	1	32	33	46
39	HDPPN86	PTA-867 10/26/99	pCMVSport 3.0	214	2042	1	2042	117	117	503	1	26	27	46
40	HDPSB18	PTA-868 10/26/99	pCMVSport 3.0	50	3408	1	3408	123	123	339	1	18	19	66
40	HDPSB18	PTA-868 10/26/99	pCMVSport 3.0	215	308	1	308		116	504	1	17	18	64
40	HDPSB18	PTA-868 10/26/99	pCMVSport 3.0	216	1568	1	1568		1525	505	1	7	8	14
40	HDPSB18	PTA-868 10/26/99	pCMVSport 3.0	217	865	1	865		345	506	1	1	2	107
41	HDPSH53	PTA-868 10/26/99	pCMVSport 3.0	51	1663	1	1663	158	158	340	1	19	20	90
41	HDPSH53	PTA-868 10/26/99	pCMVSport 3.0	218	1687	1	1687	153	153	507	1	19	20	127
41	HDPSH53	PTA-868 10/26/99	pCMVSport 3.0	219	570	1	570	212	212	508	1	19	20	90
42	HDPSP01	209745 04/07/98	pCMVSport 3.0	52	2343	1	2343	184	184	341	1	20	21	710
42	HDPSP01	209745 04/07/98	pCMVSport 3.0	220	1752	1	1752	227	227	509	1	20	21	308
43	HDPSP54	209782 04/20/98	pCMVSport 3.0	53	3091	2304	3091	2356	2356	342	1	18	19	48
43	HDPSP54	209782 04/20/98	pCMVSport 3.0	221	536	1	536	179	179	510	1	41	42	55

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
44	HDPUW68	203331 10/08/98	pCMVSport 3.0	54	1748	1	1748	40	40	343	1	18	19	467
45	HDPXY01	PTA-868 10/26/99	pCMVSport 3.0	55	766	1	766	23	23	344	1	37	38	98
45	HDPXY01	PTA-868 10/26/99	pCMVSport 3.0	222	2409	1	2409	33	33	511	1	37	38	98
45	HDPXY01	PTA-868 10/26/99	pCMVSport 3.0	223	737	1	423		539	512	1	9	10	22
45	HDPXY01	PTA-868 10/26/99	pCMVSport 3.0	224	1471	105	1471		1190	513	1	16	17	25
46	HDTBD53	PTA-848 10/13/99	pCMVSport 2.0	56	2803	1	2803	288	288	345	1	22	23	365
46	HDTBD53	PTA-848 10/13/99	pCMVSport 2.0	225	3302	1	2718	292	292	514	1	22	23	365
47	HDTBV77	203070 07/27/98	pCMVSport 2.0	57	2181	1	2181	326	326	346	1	22	23	608
48	HDTDQ23	209965 06/11/98	pCMVSport 2.0	58	2207	1	2207	132	132	347	1	20	21	56
48	HDTDQ23	209965 06/11/98	pCMVSport 2.0	226	2227	1	2206	148	148	515	1	20	21	108
48	HDTDQ23	209965 06/11/98	pCMVSport 2.0	227	2214	1	2206	148	148	516	1	20	21	73
49	HE2DE47	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	59	3533	2821	3532	808	808	348	1	30	31	540

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
49	HE2DE47	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	228	1145	435	1115	515	515	517	1	22	23	81
50	HE2NV57	209877 05/18/98	Uni-ZAP XR	60	867	1	867	99	99	349	1	36	37	99
51	HE2PH36	209603 01/29/98	Uni-ZAP XR	61	1558	1	1558	28	28	350	1	21	22	66
52	HE8DS15	PTA-1544 03/21/00	Uni-ZAP XR	62	2199	1	2199	91	91	351	1	24	25	72
53	HE9HY07	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	63	832	1	832	35	35	352	1	26	27	41
54	HEOMQ63	209563 12/18/97	pSport1	64	1336	1	1336	123	123	353	1	23	24	47
55	HEPAB80	209423 10/30/97	Uni-ZAP XR	65	799	1	799	73	73	354	1	28	29	121
55	HEPAB80	209423 10/30/97	Uni-ZAP XR	229	802	1	802	67	67	518	1	28	29	122
56	HFABH95	209407 10/23/97	Uni-ZAP XR	66	1347	1	1347	199	199	355	1	21	22	116
57	HFAEF57	209277 09/18/97	Uni-ZAP XR	67	642	1	642	232	232	356	1	42	43	86

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstA A of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
58	HFCEB37	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	68	802	352	802		487	357	1			10
59	HFFAD59	209242 09/12/97	Lambda ZAP II	69	470	1	470	44	44	358	1	17	18	45
60	HFGAD82	209225 08/28/97	Uni-ZAP XR	70	1881	772	1861	1019	1019	359	1	18	19	38
61	HFIUR10	209277 09/18/97	pSport1	71	541	1	541	50	50	360	1	22	23	44
62	HFTBM50	209300 09/25/97	Uni-ZAP XR	72	762	1	740	158	158	361	1	20	21	34
63	HFTDZ36	209300 09/25/97	Uni-ZAP XR	73	1103	231	1103	547	547	362	1	22	23	68
64	HFXBL33	203071 07/27/98	Lambda ZAP II	74	1633	1	1633	152	152	363	1	24	25	162
65	HFXJX44	209782 04/20/98	Lambda ZAP II	75	1384	1	1384	98	98	364	1	18	19	47
66	HFXKT05	209651 03/04/98	Lambda ZAP II	76	1715	1	1715	204	204	365	1	18	19	79
67	HGBHI35	209423 10/30/97	Uni-ZAP XR	77	1437	71	1276	87	87	366	1	16	17	292
68	HGLAF75	209407 10/23/97	Uni-ZAP XR	78	776	1	776	231	231	367	1	28	29	121
69	HHENV10	209368 10/16/97	pCMVSport 3.0	79	1155	1	1155	143	143	368	1	27	28	50

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstA A of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
70	HHGCG53	97899 02/26/97 209045 05/15/97	Lambda ZAP II	80	407	1	407	230	230	369	1	33	34	44
71	HHGCM76	97958 03/13/97 209072 05/22/97	Lambda ZAP II	81	711	8	711	270	270	370	1	22	23	89
71	HHGCM76	97958 03/13/97 209072 05/22/97	Lambda ZAP II	230	711	8	711	270	270	519	1			11
72	HHPEN62	209746 04/07/98	Uni-ZAP XR	82	2152	141	2152	183	183	371	1	27	28	508
73	HJABB94	209119 06/12/97	pBluescript SK-	83	1555	1	1555	74	74	372	1	28	29	77
74	HJACG30	PTA-843 10/13/99	pBluescript SK-	84	1532	1	1532	291	291	373	1	27	28	44
74	HJACG30	PTA-843 10/13/99	pBluescript SK-	231	1614	1020	1614		50	520	1	1	2	130
74	HJACG30	PTA-843 10/13/99	pBluescript SK-	232	1087	491	1087		350	521	1	1	2	122
75	HJBCY35	209877 05/18/98	pBluescript SK-	85	1559	93	1272	232	232	374	1	23	24	327
76	HJPAD75	209641 02/25/98	Uni-ZAP XR	86	1231	1	1231	60	60	375	1	29	30	91

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstA A of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
77	HKABZ65	209683 03/20/98	pCMVSport 2.0	87	1189	1	1189	77	77	376	1	17	18	243
77	HKABZ65	209683 03/20/98	pCMVSport 2.0	233	1191	1	1191	69	69	522	1	17	18	243
78	HKACB56	209346 10/09/97	pCMVSport 2.0	88	496	1	496	27	27	377	1	23	24	80
79	HKACD58	209346 10/09/97	pCMVSport 2.0	89	3153	1	3153	38	38	378	1	25	26	301
79	HKACD58	209346 10/09/97	pCMVSport 2.0	234	1626	1	1626	35	35	523	1	25	26	154
80	HKAEV06	209627 02/12/98	pCMVSport 2.0	90	2496	1	2496	501	501	379	1	30	31	438
80	HKAEV06	209627 02/12/98	pCMVSport 2.0	235	2351	1	2351	197	197	524	1	29	30	57
81	HKAFT66	PTA-849 10/13/99	pCMVSport 2.0	91	1001	270	1001	508	508	380	1	41	42	107
81	HKAFT66	PTA-849 10/13/99	pCMVSport 2.0	236	1001	270	1001	508	508	525	1	41	42	107
81	HKAFT66	PTA-849 10/13/99	pCMVSport 2.0	237	669	1	669	234	234	526	1			37
82	HKB1E57	209651 03/04/98	pCMVSport 1	92	1142	1038	1142	178	178	381	1	30	31	234
82	HKB1E57	209651 03/04/98	pCMVSport 1	238	417	1	417	30	30	527	1	26	27	46
83	HKFBC53	209782 04/20/98	ZAP Express	93	2238	1	2238	64	64	382	1	15	16	470

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
83	HKFBC53	209782 04/20/98	ZAP Express	239	1949	1	1906	41	41	528	1	18	19	442
83	HKFBC53	209782 04/20/98	ZAP Express	240	1487	1	1487		3	529	1	1	2	309
83	HKFBC53	209782 04/20/98	ZAP Express	241	1525	1	1525		3	530	1	1	2	243
84	HKGDL36	209877 05/18/98	pSport1	94	1052	1	1052	53	53	383	1	33	34	260
84	HKGDL36	209877 05/18/98	pSport1	242	1050	1	1050	55	55	531	1	33	34	148
85	HKISB57	209603 01/29/98	pBluescript	95	1492	1	1439	130	130	384	1	19	20	95
86	HKMLM11	209236 09/04/97	pBluescript	96	954	1	954	82	82	385	1	20	21	130
87	HKMMW74	209463 11/14/97	pBluescript	97	1794	1	1794	202	202	386	1	21	22	41
88	HLDON23	209628 02/12/98	pCMVSport 3.0	98	1262	208	1256	368	368	387	1	20	21	113
89	HLDQR62	203027 06/26/98	pCMVSport 3.0	99	2572	427	2572	520	520	388	1	18	19	161
90	HLDQU79	203071 07/27/98	pCMVSport 3.0	100	1488	1	1488	99	99	389	1	23	24	348
91	HLHAL68	209746 04/07/98	Uni-ZAP XR	101	704	1	704	30	30	390	1	21	22	44
92	HLIBD68	203071 07/27/98	pCMVSport 1	102	1022	1	1022	186	186	391	1	35	36	50

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstAA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
93	HLICQ90	203517 12/10/98	pCMVSport 1	103	1766	1	1766	249	249	392	1	29	30	206
94	HLTHR66	209782 04/20/98	Uni-ZAP XR	104	2286	1	2286	5	5	393	1	34	35	75
95	HLTIP94	PTA-2076 06/09/00	Uni-ZAP XR	105	1240	1	1170	226	226	394	1	26	27	97
95	HLTIP94	PTA-2076 06/09/00	Uni-ZAP XR	243	647	1	647	226	226	532	1	26	27	65
95	HLTIP94	PTA-2076 06/09/00	Uni-ZAP XR	244	1321	870	1209		3	533	1	1	2	299
96	HLWAA17	209626 02/12/98	pCMVSport 3.0	106	997	246	997	436	436	395	1	15	16	187
97	HLYAC95	203071 07/27/98	pSport1	107	312	1	312	92	92	396	1	16	17	46
98	HMADK33	209368 10/16/97	Uni-ZAP XR	108	864	1	864	161	161	397	1	24	25	152
99	HMAMI15	PTA-2075 06/09/00	Uni-ZAP XR	109	1258	1	1258	4	4	398	1	26	27	340
99	HMAMI15	PTA-2075 06/09/00	Uni-ZAP XR	245	1084	1	1084	3	3	534	1	26	27	306
100	HMCFY13	209628 02/12/98	Uni-ZAP XR	110	883	1	883	175	175	399	1	27	28	64
101	HMDAB56	209368 10/16/97	Uni-ZAP XR	111	1465	1	1465	273	273	400	1	32	33	44
102	HMEED18	209368 10/16/97	Lambda ZAP II	112	1369	28	1369	34	34	401	1	34	35	221

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstA A of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
103	HMEFT54	209243 09/12/97	Lambda ZAP II	113	596	1	596	332	332	402	1	19	20	39
104	HMEGF92	209243 09/12/97	Lambda ZAP II	114	629	1	611	92	92	403	1	27	28	62
105	HMSDL37	PTA-842 10/13/99	Uni-ZAP XR	115	2497	1	2497	531	531	404	1	26	27	64
105	HMSDL37	PTA-842 10/13/99	Uni-ZAP XR	246	1776	1	1776	528	528	535	1	26	27	64
105	HMSDL37	PTA-842 10/13/99	Uni-ZAP XR	247	784	1	784	565	565	536	1	6	7	26
105	HMSDL37	PTA-842 10/13/99	Uni-ZAP XR	248	699	275	427		2	537	1	1	2	50
106	HMSFI26	209368 10/16/97	Uni-ZAP XR	116	1217	1	1217	120	120	405	1	34	35	62
107	HMVBS81	209628 02/12/98	pSport1	117	529	1	529	34	34	406	1	43	44	139
108	HMWDC28	209126 06/19/97	Uni-ZAP XR	118	1146	105	754	124	124	407	1	30	31	42
109	HMWFT65	209368 10/16/97	Uni-ZAP XR	119	1346	1	1346	72	72	408	1	27	28	121
110	HNEEE24	209346 10/09/97	Uni-ZAP XR	120	1079	1	1079	213	213	409	1	21	22	71
111	HNFFC43	203027 06/26/98	Uni-ZAP XR	121	2103	209	2058	488	488	410	1	12	13	68
112	HNFIY77	209628 02/12/98	pBluescript	122	1212	28	1212	228	228	411	1	34	35	233

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
113	HNFJF07	209463 11/14/97	Uni-ZAP XR	123	616	1	616	86	86	412	1	21	22	66
114	HNGFR31	209407 10/23/97	Uni-ZAP XR	124	536	1	536	108	108	413	1	23	24	90
115	HNGIJ31	209236 09/04/97	Uni-ZAP XR	125	796	1	796	135	135	414	1	16	17	36
116	HNGJE50	209368 10/16/97	Uni-ZAP XR	126	1037	1	1037	77	77	415	1	36	37	46
117	HNGND37	203648 02/09/99	Uni-ZAP XR	127	841	1	841	388	388	416	1	27	28	82
118	HNGOI12	PTA-847 10/13/99	Uni-ZAP XR	128	2128	1	2128	27	27	417	1	34	35	57
118	HNGOI12	PTA-847 10/13/99	Uni-ZAP XR	249	774	1	774	27	27	538	1	34	35	57
118	HNGOI12	PTA-847 10/13/99	Uni-ZAP XR	250	1396	1	1396		596	539	1	25	26	93
119	HNHEU93	209628 02/12/98	Uni-ZAP XR	129	748	1	748	57	57	418	1	34	35	81
120	HNHFM14	209683 03/20/98	Uni-ZAP XR	130	297	1	297	38	38	419	1	28	29	80
121	HNHNB29	PTA-623 09/02/99	Uni-ZAP XR	131	1894	1	1894	40	40	420	1	20	21	53
122	HNHOD46	PTA-1543 03/21/00	Uni-ZAP XR	132	1355	1	1355	12	12	421	1	20	21	80
123	HNTBI26	209563 12/18/97	pCMVSport 3.0	133	1382	1	1382	28	28	422	1	35	36	320

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
123	HNTBI26	209563 12/18/97	pCMVSport 3.0	251	1397	1	1397	32	32	540	1	35	36	172
123	HNTBI26	209563 12/18/97	pCMVSport 3.0	252	1368	1	1368	16	16	541	1	35	36	131
124	HNTBL27	209324 10/02/97	pCMVSport 3.0	134	791	71	791	100	100	423	1	23	24	115
125	HNTCE26	PTA-1544 03/21/00	pCMVSport 3.0	135	2163	830	2163	111	111	424	1	30	31	402
125	HNTCE26	PTA-1544 03/21/00	pCMVSport 3.0	253	1763	1	1763	57	57	542	1	28	29	121
126	HNTNI01	209782 04/20/98	pSport1	136	2087	1	2087	307	307	425	1	33	34	76
126	HNTNI01	209782 04/20/98	pSport1	254	1274	1	1114	306	306	543	1	33	34	49
127	HODDF13	203069 07/27/98	Uni-ZAP XR	137	830	1	830	46	46	426	1	23	24	41
128	HODDN92	209012 04/28/97 209089 06/05/97	Uni-ZAP XR	138	1939	294	1939		434	427	1	26	27	35
129	HOFMQ33	PTA-848 10/13/99	pCMVSport 2.0	139	2410	1	2410	49	49	428	1	24	25	484
129	HOFMQ33	PTA-848 10/13/99	pCMVSport 2.0	255	2409	1	2409	48	48	544	1	24	25	484
129	HOFMQ33	PTA-848 10/13/99	pCMVSport 2.0	256	876	1	876	78	78	545	1	24	25	266

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstA A of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
129	HOFMQ33	PTA-848 10/13/99	pCMVSport 2.0	257	1586	1	1586		724	546	1			5
129	HOFMQ33	PTA-848 10/13/99	pCMVSport 2.0	258	1011	873	1011		123	547	1	1	2	84
130	HOFOC73	PTA-848 10/13/99	pCMVSport 2.0	140	1491	1	1491	18	18	429	1	18	19	129
130	HOFOC73	PTA-848 10/13/99	pCMVSport 2.0	259	1395	1	1395	23	23	548	1	18	19	67
130	HOFOC73	PTA-848 10/13/99	pCMVSport 2.0	260	270	1	270		127	549	1	4	5	14
130	HOFOC73	PTA-848 10/13/99	pCMVSport 2.0	261	2324	662	2324	142	142	550	1			6
131	HOQBJ82	PTA-845 10/13/99	Uni-ZAP XR	141	3530	1	3530	361	361	430	1	21	22	164
131	HOQBJ82	PTA-845 10/13/99	Uni-ZAP XR	262	585	64	585	102	102	551	1	24	25	161
131	HOQBJ82	PTA-845 10/13/99	Uni-ZAP XR	263	4344	1339	1942		55	552	1	1	2	325
132	HOSBY40	209551 12/12/97	Uni-ZAP XR	142	1145	1	1145	89	89	431	1	30	31	56
133	HOSDJ25	209423 10/30/97	Uni-ZAP XR	143	2214	985	2214	1076	1076	432	1	18	19	40
133	HOSDJ25	209423 10/30/97	Uni-ZAP XR	264	1258	1	1258	146	146	553	1	18	19	40
134	HPEAD79	209244 09/12/97	Uni-ZAP XR	144	813	1	813	51	51	433	1	15	16	41

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
135	HPIBO15	209563 12/18/97	Uni-ZAP XR	145	1739	1	1739	128	128	434	1	18	19	211
135	HPIBO15	209563 12/18/97	Uni-ZAP XR	265	1739	1	1739	127	127	554	1	18	19	173
136	HPJBI33	209889 05/22/98	Uni-ZAP XR	146	1677	1	1677	236	236	435	1	31	32	53
137	HPJBK12	PTA-855 10/18/99	Uni-ZAP XR	147	2648	1	2648	126	126	436	1	18	19	48
137	HPJBK12	PTA-855 10/18/99	Uni-ZAP XR	266	538	1	538	119	119	555	1	18	19	48
137	HPJBK12	PTA-855 10/18/99	Uni-ZAP XR	267	1346	1	1346		969	556	1			10
137	HPJBK12	PTA-855 10/18/99	Uni-ZAP XR	268	912	1	912	509	509	557	1			4
138	HPMDK28	209628 02/12/98	Uni-ZAP XR	148	1084	1	1084	64	64	437	1	25	26	201
138	HPMDK28	209628 02/12/98	Uni-ZAP XR	269	1177	1	1083	58	58	558	1	25	26	201
139	HPRAL78	209195 08/01/97	Uni-ZAP XR	149	2072	1	2072	62	62	438	1	29	30	420
139	HPRAL78	209195 08/01/97	Uni-ZAP XR	270	1775	1038	1775	70	70	559	1	29	30	392
139	HPRAL78	209195 08/01/97	Uni-ZAP XR	271	866	128	866	148	148	560	1	42	43	63
140	HRABA80	209889 05/22/98	pCMVSport 3.0	150	1251	1	1251	144	144	439	1	27	28	102

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstAA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
140	HRABA80	209889 05/22/98	pCMVSport 3.0	272	1237	1	1237	130	130	561	1	27	28	102
141	HRACD15	209852 05/07/98	pCMVSport 3.0	151	1539	24	1539	252	252	440	1	40	41	53
141	HRACD15	209852 05/07/98	pCMVSport 3.0	273	1681	24	1453	252	252	562	1	40	41	53
142	HRACJ35	209878 05/18/98	pCMVSport 3.0	152	2077	1	2077	132	132	441	1	24	25	472
142	HRACJ35	209878 05/18/98	pCMVSport 3.0	274	1863	8	1863	99	99	563	1	24	25	472
142	HRACJ35	209878 05/18/98	pCMVSport 3.0	275	1134	1	1134		1	564	1	1	2	178
143	HRGBL78	PTA-841 10/13/99	Uni-ZAP XR	153	2108	1	2108	30	30	442	1	27	28	359
143	HRGBL78	PTA-841 10/13/99	Uni-ZAP XR	276	626	8	626	30	30	565	1	38	39	199
143	HRGBL78	PTA-841 10/13/99	Uni-ZAP XR	277	152	1	152		11	566	1			2
143	HRGBL78	PTA-841 10/13/99	Uni-ZAP XR	278	1760	127	1760		1048	567	1	10	11	32
144	HROAJ39	PTA-2069 06/09/00	Uni-ZAP XR	154	1146	224	1146	10	10	443	1	30	31	379
144	HROAJ39	PTA-2069 06/09/00	Uni-ZAP XR	279	880	1	880	31	31	568	1	15	16	283
144	HROAJ39	PTA-2069 06/09/00	Uni-ZAP XR	280	1106	224	1106	247	247	569	1	15	16	286

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
145	HROBD68	203499 12/01/98	Uni-ZAP XR	155	1998	1	1998	122	122	444	1	22	23	48
146	HSAWD74	209126 06/19/97	Uni-ZAP XR	156	970	106	970	142	142	445	1	26	27	142
146	HSAWD74	209126 06/19/97	Uni-ZAP XR	281	646	1	646	122	122	570	1	29	30	45
147	HSDEK49	209603 01/29/98	Uni-ZAP XR	157	1782	1	1782	60	60	446	1	19	20	399
147	HSDEK49	209603 01/29/98	Uni-ZAP XR	282	1590	96	1590	126	126	571	1	21	22	305
148	HSDFJ26	203648 02/09/99	Uni-ZAP XR	158	1205	23	1179	99	99	447	1	20	21	223
148	HSDFJ26	203648 02/09/99	Uni-ZAP XR	283	1179	1	1179	99	99	572	1	19	20	72
149	HSDSB09	209145 07/17/97	pBluescript	159	809	1	809	16	16	448	1	17	18	135
149	HSDSB09	209145 07/17/97	pBluescript	284	819	1	819	22	22	573	1	17	18	121
150	HSDSE75	209324 10/02/97	pBluescript	160	1151	1	1151	160	160	449	1	18	19	181
151	HSIDJ81	209551 12/12/97	Uni-ZAP XR	161	1303	1	1303	8	8	450	1	22	23	58
152	HSKDA27	PTA-322 07/09/99	Uni-ZAP XR	162	4412	1	4412	786	786	451	1	24	25	950
152	HSKDA27	PTA-322 07/09/99	Uni-ZAP XR	285	1792	134	1792	127	127	574	1	21	22	509

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstA A of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
152	HSKDA27	PTA-322 07/09/99	Uni-ZAP XR	286	1673	1	1673	12	12	575	1	21	22	554
153	HSKGN81	97977 04/04/97 209082 05/29/97	pBluescript	163	1907	151	1432	353	353	452	1	23	24	260
153	HSKGN81	97977 04/04/97 209082 05/29/97	pBluescript	287	2084	335	2084	537	537	576	1	18	19	23
154	HSNAD72	209139 07/03/97	Uni-ZAP XR	164	861	1	861	220	220	453	1	19	20	35
155	HSNMC45	209300 09/25/97	Uni-ZAP XR	165	587	1	587	225	225	454	1	18	19	55
155	HSNMC45	209300 09/25/97	Uni-ZAP XR	288	720	1	720	232	232	577	1	17	18	25
156	HSQFP66	209126 06/19/97	Uni-ZAP XR	166	477	1	477	96	96	455	1	32	33	78
157	HSRFZ57	PTA-622 09/02/99	Uni-ZAP XR	167	1930	1	1925	82	82	456	1	18	19	41
158	HSUBW09	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	168	1021	1	1021	153	153	457	1	31	32	56
159	HSVBU91	209603 01/29/98	Uni-ZAP XR	169	727	1	727	256	256	458	1	18	19	90

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstA A of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
160	HTAEE28	PTA-843 10/13/99	Uni-ZAP XR	170	1341	1	1341	319	319	459	1	33	34	282
160	HTAEE28	PTA-843 10/13/99	Uni-ZAP XR	289	738	159	738	372	372	578	1	33	34	122
160	HTAEE28	PTA-843 10/13/99	Uni-ZAP XR	290	935	1	807		124	579	1	1	2	'216
161	HTECC05	209877 05/18/98	Uni-ZAP XR	171	839	1	839	13	13	460	1	15	16	178
161	HTECC05	209877 05/18/98	Uni-ZAP XR	291	871	1	871	21	21	580	1	15	16	127
161	HTECC05	209877 05/18/98	Uni-ZAP XR	292	881	1	881	27	27	581	1	15	16	164
162	HTEEB42	97922 03/07/97 209070 05/22/97	Uni-ZAP XR	172	1022	20	1022	59	59	461	1	22	23	298
163	HTEFU65	209324 10/02/97	Uni-ZAP XR	173	1028	1	1028	231	231	462	1	24	25	46
164	HTELP17	203648 02/09/99	Uni-ZAP XR	174	808	1	808	164	164	463	1	20	21	44
165	HTELS08	PTA-1544 03/21/00	Uni-ZAP XR	175	1898	1	1898	15	15	464	1	17	18	158
166	HTLEP53	209641 02/25/98	Uni-ZAP XR	176	818	1	818	73	73	465	1	43	44	101
167	HTPCS72	209423 10/30/97	Uni-ZAP XR	177	3435	2141	3431	2365	2365	466	1	29	30	71

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstAA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
167	HTPCS72	209423 10/30/97	Uni-ZAP XR	293	1598	306	1598	530	530	582	1	29	30	71
168	HTPIH83	PTA-871 10/26/99	Uni-ZAP XR	178	1481	1	1481	118	118	467	1	24	25	230
168	HTPIH83	PTA-871 10/26/99	Uni-ZAP XR	294	530	1	530	111	111	583	1	24	25	140
168	HTPIH83	PTA-871 10/26/99	Uni-ZAP XR	295	1046	359	1046		96	584	1	1	2	86
169	HTSEW17	209138 07/03/97	pBluescript	179	652	1	652	170	170	468	1	34	35	37
170	HTTBI76	209641 02/25/98	Uni-ZAP XR	180	1711	1	1711	133	133	469	1	22	23	133
171	HTTBS64	PTA-841 10/13/99	Uni-ZAP XR	181	2058	1	2058	95	95	470	1	17	18	42
171	HTTBS64	PTA-841 10/13/99	Uni-ZAP XR	296	819	1	819	100	100	585	1	17	18	42
171	HTTBS64	PTA-841 10/13/99	Uni-ZAP XR	297	501	1	501		175	586	1	1	2	76
172	HTXJM03	209580 01/14/98	Uni-ZAP XR	182	2398	211	2398	328	328	471	1	18	19	56
173	HTXON32	203648 02/09/99	Uni-ZAP XR	183	1505	1	1505	72	72	472	1	22	23	52
174	HUFCJ30	209641 02/25/98	pSport1	184	868	1	868	123	123	473	1	29	30	50
175	HUVEB53	209603 01/29/98	Uni-ZAP XR	185	1502	1	1502	14	14	474	1	20	21	45

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO:X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO:Y	FirstAA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
176	HWAAD63	203570 01/11/99	pCMVSport 3.0	186	3308	1	3308	322	322	475	1	30	31	168
176	HWAAD63	203570 01/11/99	pCMVSport 3.0	298	3306	1	3306	322	322	587	1	30	31	53
176	HWAAD63	203570 01/11/99	pCMVSport 3.0	299	2194	1	2194	312	312	588	1	30	31	169
177	HWADJ89	PTA-1543 03/21/00	pCMVSport 3.0	187	1769	529	1769	581	581	476	1	1	2	43
178	HWBFX31	PTA-1543 03/21/00	pCMVSport 3.0	188	1677	1	1677	271	271	477	1	1	2	52

Table 1B (Comprised of Tables 1B.1 and 1B.2)

The first column in Table 1B.1 and Table 1B.2 provides the gene number in the application corresponding to the clone identifier. The second column in Table 1B.1 and Table 1B.2 provides a unique "Clone ID:" for the cDNA clone related to each contig sequence disclosed in Table 1B.1 and Table 1B.2. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO:X as determined by directly sequencing the referenced clone. The referenced clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases, however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length cDNA can be obtained by methods described elsewhere herein. The third column in Table 1B.1 and Table 1B.2 provides a unique "Contig ID" identification for each contig sequence. The fourth column in Table 1B.1 and Table 1B.2 provides the "SEQ ID NO:" identifier for each of the contig polynucleotide sequences disclosed in Table 1B.

Table 1B.1

The fifth column in Table 1B.1, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred open reading frame (ORF) shown in the sequence listing and referenced in Table 1B.1, column 6, as SEQ ID NO:Y. Where the nucleotide position number "To" is lower than the nucleotide position number "From", the preferred ORF is the reverse complement of the referenced polynucleotide sequence. The sixth column in Table 1B.1 provides the corresponding SEQ ID NO:Y for the polypeptide sequence encoded by the preferred ORF delineated in column 5. In one embodiment, the invention provides an amino acid sequence comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated by "ORF (From-To)". Also provided are polynucleotides encoding such amino acid sequences and the complementary strand thereto. Column 7 in Table 1B.1 lists residues comprising epitopes contained in the polypeptides encoded by the preferred ORF (SEQ ID NO:Y), as predicted using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, at least one, two, three, four, five or more of the predicted epitopes as described in Table 1B. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly.

Column 8 in Table 1B.1 provides a chromosomal map location for certain polynucleotides of the invention. Chromosomal location was determined by finding exact matches to

EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Each sequence in the UniGene database is assigned to a "cluster"; all of the ESTs, cDNAs, and STSs in a cluster are believed to be derived from a single gene. Chromosomal mapping data is often available for one or more sequence(s) in a UniGene cluster; this data (if consistent) is then applied to the cluster as a whole. Thus, it is possible to infer the chromosomal location of a new polynucleotide sequence by determining its identity with a mapped UniGene cluster.

A modified version of the computer program BLASTN (Altshul, et al., J. Mol. Biol. 215:403-410 (1990), and Gish, and States, Nat. Genet. 3:266-272) (1993) was used to search the UniGene database for EST or cDNA sequences that contain exact or near-exact matches to a polynucleotide sequence of the invention (the 'Query'). A sequence from the UniGene database (the 'Subject') was said to be an exact match if it contained a segment of 50 nucleotides in length such that 48 of those nucleotides were in the same order as found in the Query sequence. If all of the matches that met this criteria were in the same UniGene cluster, and mapping data was available for this cluster, it is indicated in Table 1B under the heading "Cytologic Band". Where a cluster had been further localized to a distinct cytologic band, that band is disclosed; where no banding information was available, but the gene had been localized to a single chromosome, the chromosome is disclosed.

Once a presumptive chromosomal location was determined for a polynucleotide of the invention, an associated disease locus was identified by comparison with a database of diseases which have been experimentally associated with genetic loci. The database used was the Morbid Map, derived from OMIM™ and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000;. If the putative chromosomal location of a polynucleotide of the invention (Query sequence) was associated with a disease in the Morbid Map database, an OMIM reference identification number was noted in column 9, Table 1B.1, labelled "OMIM Disease Reference(s). Table 5 is a key to the OMIM reference identification numbers (column 1), and provides a description of the associated disease in Column 2.

Table 1B.2

Column 5, in Table 1B.2, provides an expression profile and library code:count for each of the contig sequences (SEQ ID NO:X) disclosed in Table 1B, which can routinely be combined with the information provided in Table 4 and used to determine the tissues, cells, and/or cell line libraries which predominantly express the polynucleotides of the invention. The first number in Table 1B.2, column 5 (preceding the colon), represents the tissue/cell source identifier code corresponding to the code and description provided in Table 4. The second number in column 5 (following the colon) represents the number of times a sequence corresponding to the reference polynucleotide sequence was identified in the corresponding tissue/cell source. Those tissue/cell source identifier codes in

which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of ^{33}P dCTP, using oligo (dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression.

Table 1B.1

Gene No:	cDNA Clone ID	Contig ID:	SEQ ID NO: X	ORF (From-To)	AA SEQ ID NO: Y	Predicted Epitopes	Cytologic Band	OMIM Disease Reference(s):
1	H2CBU83	884134	11	157 - 777	300	Pro-62 to Asp-67, Arg-74 to Gly-80, Gln-146 to Glu-168.	11p14-p13	102772, 106210, 106210, 106210, 106210, 107271, 114550, 115500, 136530, 151390, 179615, 179615, 179616, 180385, 194070, 194070, 194070, 245349, 602092
	H2CBU83	745366	189	157 - 312	478			
2	H6EDC19	543259	12	389 - 733	301	Arg-5 to Pro-12.		
3	HACBD91	637482	13	117 - 266	302		3q13.33	600882
4	HAGAQ26	561996	14	251 - 439	303		7q33	180105, 222800
5	HAGDS35	1352199	15	45 - 410	304	Leu-31 to Phe-38, Glu-47 to Trp-52.		
	HAGDS35	543617	190	52 - 405	479	Leu-31 to Phe-38, Glu-47 to Trp-52.		
6	HAJAN23	1352364	16	109 - 1797	305	Pro-186 to Tyr-196, Leu-294 to Leu-300, Ser-380 to Thr-385, Thr-486 to Ser-499, Phe-513 to Ser-522.	5q12-q13	126060, 143200, 143200, 181510, 253200, 268800, 268800, 600354, 600354, 600354, 600887
	HAJAN23	872551	191	120 - 629	480			
7	HAJBR69	638516	17	262 - 423	306			
8	HAMFE15	905695	18	1495 - 2757	307	Leu-8 to Thr-16, Gly-93 to Ala-105, Arg-136 to Thr-142, Lys-195 to Gln-200, Lys-241 to His-247, Gly-255 to Gln-270, Gln-288 to Leu-293, Thr-316 to Asp-328,	7q34	180105, 222800, 274180

						Gly-348 to Pro-355, Asp-408 to Met-415.		
	HAMFE15	823350	192	226 - 369	481	Ser-39 to Asn-47.		
9	HAMGR28	892971	19	98 - 823	308	Ala-27 to Asp-34, Tyr-116 to Leu-125.		
	HAMGR28	748223	193	40 - 651	482	Ala-27 to Asp-34, Tyr-116 to Leu-125, Arg-185 to Cys-194.		
10	HAPOM49	769555	20	251 - 817	309	Gln-23 to Asp-30, Lys-66 to Cys-87.		
	HAPOM49	722386	194	448 - 816	483	Met-1 to Cys-21, Cys-41 to Asp-59, Pro-104 to His-116.		
11	HATBR65	635514	21	252 - 446	310	Ile-25 to Trp-30.		
12	HAUAI83	639009	22	253 - 399	311	Asn-34 to Lys-42.	19	
	HAUAI83	383592	195	575 - 643	484	Ala-17 to Lys-23.		
13	HBAMB15	671835	23	390 - 569	312		2p16	126600, 126600, 136435, 160980, 600678
14	HBGBA69	1352289	24	124 - 843	313	Pro-51 to Asp-56, Gly-95 to Thr-105, Val-132 to Ala-138, Pro-229 to Leu-240.		
	HBGBA69	709658	196	62 - 244	485	Thr-52 to Gly-57.		
15	HBIAE26	514418	25	75 - 194	314	Ser-22 to Lys-27.		
16	HBINS58	1352386	26	57 - 578	315	Gly-32 to Gly-37, Glu-78 to His-87, Tyr-102 to Ala-107, Pro-115 to Val-122, Lys-164 to Tyr-170.	1	
	HBINS58	961712	197	71 - 592	486	Gly-32 to Gly-37, Glu-78 to His-87, Tyr-102 to Ala-107, Pro-115 to Val-122,		

						Lys-164 to Gln-171.		
	HBINS58	892924	198	100 - 732	487	Gly-32 to Gly-37, Glu-78 to His-87, Tyr-102 to Ala-107, Pro-115 to Val-122.		
17	HBNAW17	526797	27	77 - 262	316			
18	HCE2F54	634016	28	166 - 1125	317	His-44 to Pro-50, Glu-90 to Glu-96, Gln-111 to Glu-117, Ser-143 to Gly-151, Ala-154 to Leu-166, Pro-199 to Ala-216, Gly-264 to Asp-272.	16q22.1	103850, 114835, 116800, 140100, 140100, 192090, 192090, 192090, 192090, 245900, 245900, 276600, 600223
19	HCE3G69	728432	29	165 - 1175	318	Lys-50 to Asp-66, Pro-68 to Glu-77, Glu-102 to Glu-107, Glu-131 to Leu-146, Ala-175 to Glu-183, Phe-205 to Lys-216, Val-263 to Thr-281, Pro-304 to Ala-313.	2q36.1	120070, 120131, 120131, 138030, 259900
	HCE3G69	494346	199	165 - 482	488	Lys-50 to Leu-69.		
20	HCE5F43	612796	30	113 - 931	319	Asn-23 to Ser-32, Trp-61 to Ser-68, Ala-130 to Ala-135, Thr-141 to Gly-148, Asn-176 to Gly-182, Pro-197 to Glu-205, His-211 to Glu-222, Gln-242 to Ile-248, Thr-265 to Leu-271.	10p13	601362
21	HCEFB80	1143407	31	12 - 281	320	Met-1 to Ala-8, Ser-51 to Leu-62,	22q13.33	

						Pro-70 to Lys-78.		
	HCEFB80	1046853	200	5 - 274	489	Met-1 to Ala-8.		
22	HCEWE20	543370	32	166 - 321	321	Ser-17 to Gln-22.		
23	HCGMD59	636078	33	438 - 662	322			
24	HCNDR47	1016919	34	21 - 401	323	Pro-71 to His-92.	1	
	HCNDR47	863677	201	124 - 507	490	Pro-71 to His-92.		
	HCNDR47	874128	202	603 - 632	491	Leu-1 to Thr-9.		
25	HCNSM70	637547	35	107 - 751	324	Met-1 to Ser-6.	11q24	600359, 602574, 602574
	HCNSM70	589445	203	161 - 436	492	Met-1 to Ser-6.		
26	HCUIM65	550208	36	557 - 700	325			
27	HCWDS72	707833	37	19 - 318	326			
28	HCWKC15	553621	38	37 - 159	327	Lys-28 to Thr-34.		
29	HDHEB60	499233	39	568 - 894	328	Asp-48 to Ser-54.	11p11.2	133701, 168500, 171650, 176930, 176930, 600623, 600811, 600958
30	HDPBA28	1062783	40	259 - 3084	329	Gln-33 to Trp-49, Gly-161 to Gly-172, Ile-207 to Arg-212, Asn-414 to Val-419, Val-423 to Gln-428, Val-436 to Gly-441, Lys-467 to Leu-478, Phe-497 to Ser-508, Met-550 to Gly-560, Glu-688 to Thr-697, Ile-711 to Gly-720, Ala-747 to Gly-759, Leu-785 to Phe-791, Ser-795 to Gln-800, Thr-808 to Lys-813, Ser-821 to Phe-832, Thr-879 to Glu-889, Leu-898 to Gln-904,	5q14.3	

						Gln-934 to Met-941.		
	HDPBA28	866429	204	69 - 2894	493	Gln-33 to Trp-49, Gly-161 to Gly-172, Ile-207 to Arg-212, Asn-414 to Val-419, Val-423 to Gln-428, Val-436 to Gly-441, Lys-467 to Leu-478, Phe-497 to Ser-508, Met-550 to Gly-560, Glu-688 to Thr-697, Ile-711 to Gly-720, Ala-747 to Gly-759, Leu-785 to Phe-791, Ser-795 to Gln-800.		
31	HDPCL63	1019008	41	35 - 835	330	Ile-4 to Glu-10, Gly-58 to Asp-64.		
	HDPCL63	847045	205	260 - 733	494	Lys-72 to Cys-80, Leu-90 to Pro-96, Ala-110 to Thr-119, Glu-121 to Gly-128, Ser-140 to Lys-147.		
	HDPCL63	897484	206	605 - 961	495	Pro-8 to Gln-13, Thr-38 to Pro-46, Pro-100 to Met-108, Pro-113 to Pro-118.		
32	HDPCO25	460682	42	182 - 343	331	Pro-22 to His-33, Ser-42 to Trp-48.		
33	HDPFP29	628254	43	293 - 451	332			
34	HDPGT01	771583	44	8 - 271	333	Cys-65 to Ser-71.	16q22.1	103850, 114835, 116800, 140100, 140100, 192090, 192090, 192090, 192090, 245900, 245900, 276600, 600223

35	HDPHI51	460679	45	245 - 367	334	Gly-2 to Glu-7, Arg-27 to Gly-34.		
36	HDPJM30	879325	46	59 - 1633	335	Arg-15 to Val-22.	21q22.3	120220, 120240, 123580, 151385, 171860, 190685, 236100, 236200, 240300, 267750, 600065, 601072, 601145
	HDPJM30	603517	207	259 - 438	496	Pro-41 to Ala-55.		
37	HDPMM88	972734	47	100 - 2913	336	Met-1 to Ser-13, Ser-45 to Phe-51, Asn-103 to Lys-113, Phe-135 to Gly-140, Asp-165 to Pro-178, Ser-224 to Ala-229, Asn-283 to Arg-288, Asp-347 to Tyr-352, Thr-367 to Glu-372, Gly-420 to Thr-425, Glu-456 to Lys-462, Phe-466 to Asn-474, Glu-480 to Leu-485, Asp-673 to Asp-681, Gln-684 to Gly-689, Leu-841 to Gly-874, Gly-890 to Pro-900, Ser-902 to Ser-911, Leu-918 to Asp-924, Ser-930 to Val-935.		
	HDPMM88	906121	208	141 - 467	497	Ser-28 to Phe-34, Asn-86 to Tyr-93.		
	HDPMM88	902299	209	44 - 181	498			
	HDPMM88	885059	210	419 - 439	499			
	HDPMM88	874074	211	111 - 146	500			
	HDPMM88	854246	212	167 - 334	501			

	HDPMM88	854245	213	28 - 186	502	Ser-26 to Thr-31.		
38	HDPOJ08	731863	48	159 - 527	337	Lys-30 to Thr-35.	3q25.33	222900
39	HDPPN86	1037893	49	127 - 267	338			
	HDPPN86	895711	214	117 - 257	503			
40	HDPSB18	1043263	50	123 - 323	339	Lys-23 to Lys-31, Ala-38 to Ser-43.	10	
	HDPSB18	903816	215	116 - 307	504			
	HDPSB18	905414	216	1525 - 1566	505			
	HDPSB18	732097	217	345 - 665	506	Lys-57 to Gly-64.		
41	HDPSH53	1309174	51	158 - 430	340	Met-1 to Trp-6, Leu-22 to Thr-27, Pro-44 to Thr-63.		
	HDPSH53	1040056	218	153 - 536	507	Met-1 to Trp-6, Leu-22 to Thr-27, Pro-44 to Gly-58, Ala-61 to Glu-74, Pro-99 to Gly-111, Cys-121 to Ser-127.		
	HDPSH53	882768	219	212 - 484	508	Met-1 to Trp-6, Leu-22 to Thr-27.		
42	HDPSP01	1352280	52	184 - 2313	341	Gln-75 to Cys-80, Glu-97 to Lys-104, Glu-114 to Ala-119, Thr-177 to Gln-190, Asn-230 to Trp-240, Glu-269 to Arg-274, Pro-279 to Ala-286, Pro-323 to Cys-328, Asn-362 to Leu-367, Thr-390 to Arg-397, Leu-490 to Arg-495, Gln-556 to Leu-561,		

						Gln-657 to Val-674.		
	HDPSP01	689129	220	227 - 1153	509	Gln-75 to Cys-80.		
43	HDPSP54	744440	53	2356 - 2499	342	Pro-29 to Lys-37.	1q21.2	104770, 107670, 110700, 145001, 146760, 146790, 191315, 601412, 601652, 601863, 602491
	HDPSP54	502472	221	179 - 343	510			
44	HDPUW68	812737	54	40 - 1440	343	Gly-12 to Tyr-26, Val-52 to Asp-59, Gln-88 to Asp-93, Arg-124 to Asn-129, His-193 to Arg-198, Gln-207 to Thr-213, Gln-338 to Arg-346, Ser-378 to Ala-384, Ser-413 to Arg-420, Ser-428 to Glu-434, His-443 to Ser-451, Glu-454 to Ser-461.		
45	HDPXY01	879048	55	23 - 319	344	Pro-39 to Trp-44.	17	
	HDPXY01	904768	222	33 - 329	511	Pro-39 to Trp-44.		
	HDPXY01	895716	223	539 - 607	512			
	HDPXY01	895715	224	1190 - 1267	513			
46	HDTBD53	972757	56	288 - 1385	345	Glu-91 to Arg-117, Lys-124 to Ser-136, Tyr-191 to Glu-200, Glu-265 to Lys-272.	3p25.1	193300, 193300, 227646
	HDTBD53	906342	225	292 - 1389	514	Glu-91 to Arg-117, Lys-124 to Ser-136.		
47	HDTBV77	785879	57	326 - 2149	346	Lys-5 to Lys-10, Asn-33 to Lys-39, Asp-48 to Lys-54, Pro-62 to Asp-67,	10p15.1	

						Asn-116 to Arg-123, His-157 to Ala-162, Val-242 to Lys-249, Val-251 to Asp-264.		
48	HDTDQ23	1306984	58	132 - 302	347	Arg-24 to Arg-31, Ile-33 to Trp-41, Met-43 to His-52.		
	HDTDQ23	879009	226	148 - 471	515	Arg-24 to Arg-31, Ile-33 to Gly-41.		
	HDTDQ23	751707	227	148 - 369	516	Arg-24 to Arg-31.		
49	HE2DE47	619852	59	808 - 2427	348	Leu-9 to Tyr-15, Asp-34 to Gln-46, Pro-51 to Asp-57, Gly-88 to Thr-104, Thr-123 to Ser-128.		
	HE2DE47	382025	228	515 - 757	517	Leu-31 to Asn-38.		
50	HE2NV57	740750	60	99 - 398	349	Ala-84 to Gln-93.		
51	HE2PH36	570903	61	28 - 228	350			
52	HE8DS15	847060	62	91 - 309	351		18	
53	HE9HY07	420063	63	35 - 160	352	Pro-35 to Phe-41.		
54	HEOMQ63	603533	64	123 - 266	353		20p12.1	
55	HEPAB80	1307790	65	73 - 438	354	Met-1 to Pro-6, Glu-58 to Cys-63, Glu-65 to Gly-72, Thr-74 to Asn-88, Tyr-104 to Trp-109.		
	HEPAB80	570048	229	67 - 435	518	Met-1 to Pro-6, Glu-58 to Cys-63, Glu-65 to Gly-72, Thr-74 to Val-87.		
56	HFABH95	566712	66	199 - 549	355			
57	HFAEF57	534142	67	232 - 492	356	Leu-69 to Leu-74.		

58	HFCEB37	411345	68	487 - 519	357			
59	HFFAD59	520369	69	44 - 181	358	Lys-13 to Asn-19, Asn-27 to Asn-35.	4q32-q34	189800, 208400, 231675
60	HFGAD82	513669	70	1019 - 1135	359		Xp22.2	300075, 300077, 301200, 302350, 302801, 305435, 306000, 306000, 307800, 308800, 309510, 311200, 312040, 312170, 312700, 313400
61	HFIUR10	532060	71	50 - 184	360	Gln-31 to Pro-39.		
62	HFTBM50	545012	72	158 - 262	361	Ala-19 to Lys-34.	4q12	103600, 103600, 103600, 104150, 104150, 104500, 164920, 164920, 164920, 170650, 600900
63	HFTDZ36	545726	73	547 - 753	362		16q24.3	155555, 155555, 227650, 253000, 602783
64	HFXBL33	778070	74	152 - 640	363			
65	HFXJX44	701988	75	98 - 241	364			
66	HFXKT05	658690	76	204 - 443	365	Leu-16 to Ser-23, Ser-38 to Pro-43, Gly-53 to Leu-60.	1p34.1	120550, 120570, 120575, 121800, 130500, 133200, 138140, 171760, 171760, 178300, 255800
67	HGBHI35	570262	77	87 - 965	366	Pro-10 to Arg-15, Leu-96 to Ser-103, Gly-172 to Pro-178, Gln-213 to Asp-218, Asn-268 to Leu-275, Arg-282 to Phe-289.	1p32.2	120260, 138140, 178300
68	HGLAF75	566838	78	231 - 596	367	Ser-40 to Gly-45, Leu-73 to Arg-80.		
69	HHENV10	562772	79	143 - 295	368	Asp-26 to Leu-36, Leu-42 to Phe-50.		
70	HHGCG53	340818	80	230 - 361	369		8	
71	HHGCM76	662329	81	270 - 536	370		17	
	HHGCM76	383547	230	270 - 302	519			
72	HHPEN62	695134	82	183 - 1709	371	Met-98 to Gln-107, Gly-120 to Gly-126,		

						Pro-138 to Trp-145, Leu-159 to Gly-169, Val-211 to Arg-217, Cys-256 to His-262, Glu-320 to Val-327, Phe-399 to Asn-406, Asp-444 to Ser-450, Asp-475 to Trp-488.		
73	HJABB94	456466	83	74 - 307	372	Ala-28 to His-41, Pro-43 to Gln-64.	13q14.12	180200, 180200, 180200, 180200, 600631
74	HJACG30	895505	84	291 - 425	373	Thr-26 to Asn-39.	15,X	
	HJACG30	821341	231	50 - 439	520	Pro-57 to Pro-64.		
	HJACG30	774300	232	350 - 715	521	Lys-1 to Gly-8.		
75	HJBCY35	719729	85	232 - 1215	374	Glu-35 to His-41, Ser-62 to Ala-67, Pro-145 to Leu-155, Glu-157 to Ser-163, Arg-190 to Val-197, Asp-208 to Pro-215, Ser-247 to Pro-252.	7p22.3	
76	HJPAD75	651337	86	60 - 335	375	Pro-42 to Cys-50, Leu-61 to Ala-66.		
77	HKABZ65	862030	87	77 - 808	376	Ser-25 to Ala-31, Gln-146 to Ser-151, His-231 to Asn-236.		
	HKABZ65	665424	233	69 - 800	522	Ser-25 to Ala-31, Gln-146 to Ser-151, His-231 to Asn-236.		
78	HKACB56	554616	88	27 - 269	377	Tyr-39 to Lys-58.		
79	HKACD58	1352202	89	38 - 940	378	Thr-42 to Pro-53, Val-78 to Glu-86, Glu-103 to Met-112,		

						Ala-124 to Gly-131, Trp-158 to Glu-168, Gln-189 to Phe-210, Ala-221 to Gly-226, Arg-274 to Asp-284, Ala-294 to Gly-299.		
	HKACD58	552465	234	35 - 499	523	Thr-42 to Pro-53, Val-78 to Glu-86, Glu-103 to Met-112, Ala-124 to Gly-131.		
80	HKAEV06	1352263	90	501 - 1814	379	Thr-6 to Trp-13, Thr-75 to Gln-80, Thr-112 to Tyr-117, Leu-133 to Pro-138, Ala-146 to Phe-153, Gln-319 to Ser-325, Val-354 to His-372, Pro-391 to Gly-396, Val-405 to Thr-412, Ile-425 to Asp-437.		
	HKAEV06	638238	235	197 - 370	524	Thr-6 to Trp-13.		
81	HKAFT66	946512	91	508 - 831	380	Ser-51 to Thr-57.		
	HKAFT66	889258	236	508 - 831	525	Ser-51 to Thr-57.		
	HKAFT66	904790	237	234 - 347	526	Gln-23 to Asp-28.		
82	HKB1E57	876571	92	178 - 879	381	Ser-7 to Pro-14, Arg-47 to Arg-52, His-117 to Val-123, Glu-142 to Thr-149, Leu-162 to Ala-167, Gly-172 to Asn-177, Thr-226 to Ala-232.		
	HKB1E57	654871	238	30 - 170	527	Met-1 to Tyr-6,		

						Thr-38 to Ala-44.		
83	HKFBC53	1352286	93	64 - 1473	382	Arg-52 to Ala-58, Thr-121 to Lys-126, Gly-156 to Gln-164, Gly-201 to Glu-215, Thr-432 to Gly-450, Glu-461 to Gly-466.		
	HKFBC53	701893	239	41 - 1369	528	Ala-28 to Ala-33, Arg-38 to Leu-48, Thr-120 to Lys-125, Gly-155 to Gln-163, Gly-200 to Glu-214.		
	HKFBC53	513190	240	3 - 929	529	Ala-1 to Gly-6, Ala-10 to Tyr-18.		
	HKFBC53	383426	241	3 - 731	530	Ala-1 to Gly-6, Ala-10 to Tyr-18.		
84	HKGDL36	877489	94	53 - 835	383	Pro-36 to Gly-42, Gly-54 to Arg-65, Ala-85 to Ala-91, Ala-95 to Gln-102, Ala-115 to Pro-121, Pro-166 to Asp-191, Lys-243 to Ala-249.	Xp11.23	300047, 300071, 300110, 300600, 301000, 301000, 301830, 309470, 309500, 309610, 309850, 311050, 312060
	HKGDL36	704088	242	55 - 501	531	Pro-36 to Gly-42, Pro-64 to Ala-76, Gly-83 to Ala-90, Ser-100 to Cys-108, Thr-126 to Ser-135.		
85	HKISB57	625956	95	130 - 417	384	Ala-23 to Arg-36, His-38 to Ala-46, Pro-50 to Gly-56, Arg-85 to Val-94.	22q12.2	101000, 101000, 101000, 101000, 123620, 138981, 188826, 600850, 601669

86	HKMLM11	514788	96	82 - 474	385	Ala-59 to Thr-68, Glu-72 to Ser-108, Glu-115 to Lys-126.		
87	HKMMW74	581399	97	202 - 327	386			
88	HLDON23	636083	98	368 - 709	387	Arg-28 to Gln-36.	15q23	118485, 151670, 231680, 272800, 272800, 272800, 276700, 600374, 601780
89	HLDQR62	753742	99	520 - 1005	388	Arg-122 to Ser-139, Met-144 to Glu-149.	5p15.2-p14.1	123000, 602568
90	HLDQU79	740755	100	99 - 1142	389	Leu-68 to Lys-74, Tyr-109 to Lys-115, Gln-200 to Val-205, Lys-207 to Lys-214, Glu-237 to Ile-244, Ala-271 to Thr-279, Ser-317 to Ser-329, Gln-342 to Gly-348.	10q21-q22	126090, 129010, 142600, 154545, 250850, 601386, 601493
91	HLHAL68	684216	101	30 - 164	390	Leu-32 to His-38.		
92	HLIBD68	778073	102	186 - 338	391	Met-37 to Ser-43.		
93	HLICQ90	791828	103	249 - 869	392	Pro-55 to Gly-66, Phe-92 to Leu-103.		
94	HLTHR66	699812	104	5 - 232	393			
95	HLTIP94	1087335	105	226 - 516	394	Gly-4 to Glu-9, Asp-22 to Cys-28, Glu-39 to Leu-44, Phe-88 to Phe-94.	17	
	HLTIP94	1035443	243	226 - 423	532	Gly-4 to Glu-9.		
	HLTIP94	1047690	244	3 - 899	533	Gly-1 to Glu-8, Gly-37 to Gly-61, Gln-71 to Phe-81, Asp-95 to Gly-103, Leu-126 to Ile-131, Val-166 to Glu-171.		

96	HLWAA17	629552	106	436 - 996	395	Lys-17 to Glu-27, Gln-40 to Gly-47.	1q21	104770, 107670, 110700, 135940, 145001, 146790, 152445, 152445, 159001, 174000, 179755, 182860, 182860, 182860, 191315, 230800, 230800, 266200, 600897, 601105, 601412, 601652, 602491
97	HLYAC95	778075	107	92 - 232	396			
98	HMADK33	561941	108	161 - 619	397	Gly-43 to Gly-55.	16p13	138760, 186580, 249100, 266600, 600760, 600760, 600761, 600761
99	HMAMI15	1352406	109	4 - 1023	398	Gly-33 to Lys-41, Pro-52 to Lys-60, Asn-81 to Ala-86, Lys-156 to Met-164, Gln-283 to Lys-292, Glu-303 to Gly-308.		
	HMAMI15	1049263	245	3 - 923	534	Gly-33 to Lys-41, Pro-52 to Lys-60, Asn-81 to Ala-86.		
100	HMCFY13	635301	110	175 - 369	399			
101	HMDAB56	560676	111	273 - 407	400			
102	HMEED18	560775	112	34 - 699	401	Gln-85 to Lys-91, Pro-106 to Ser-117, Pro-124 to Ala-130, Trp-154 to Trp-160.		
103	HMEFT54	520307	113	332 - 451	402			
104	HMEGF92	520304	114	92 - 280	403	Ser-34 to Ser-39.		
105	HMSDL37	973996	115	531 - 725	404	Ser-31 to Lys-45, Pro-47 to Pro-53, Ser-58 to Arg-63.	3,3p	
	HMSDL37	895429	246	528 - 722	535	Ser-31 to Lys-45, Pro-47 to Pro-53, Ser-58 to Arg-63.		
	HMSDL37	904241	247	565 - 645	536			

	HMSDL37	750927	248	2 - 151	537			
106	HMSFI26	560229	116	120 - 308	405			
107	HMVBS81	639203	117	34 - 453	406		11q13	102200, 106100, 131100, 131100, 131100, 133780, 147050, 153700, 161015, 164009, 168461, 168461, 168461, 180721, 180840, 191181, 193235, 209901, 232600, 259700, 259770, 600045, 600319, 600528, 601884
108	HMWDC28	460487	118	124 - 252	407			
109	HMWFT65	562063	119	72 - 437	408			
110	HNEEE24	553558	120	213 - 428	409			
111	HNFFC43	753337	121	488 - 691	410	Asp-21 to Ser-29.	12q13.12	120140, 120140, 120140, 120140, 120140, 120140, 120140, 126337, 600808, 601284, 601769, 601769, 602116
112	HNFIY77	634551	122	228 - 929	411	Pro-47 to Met-53, Ser-130 to Ser-138.		
113	HNFJF07	577013	123	86 - 286	412	Val-25 to Gly-33.		
114	HNGFR31	553552	124	108 - 380	413			
115	HNGIJ31	519120	125	135 - 245	414	Pro-18 to Glu-25.		
116	HNGJE50	561568	126	77 - 217	415			
117	HNGND37	839224	127	388 - 636	416	Asn-46 to Ser-54.		
118	HNGOI12	1041375	128	27 - 200	417	Met-1 to Gly-9.	11	
	HNGOI12	838184	249	27 - 200	538	Met-1 to Gly-9.		
	HNGOI12	839283	250	596 - 877	539			
119	HNHEU93	634851	129	57 - 302	418			
120	HNHFM14	664507	130	38 - 280	419	Glu-67 to Ala-74.	1	
121	HNHNB29	895462	131	40 - 201	420	Glu-17 to Lys-30, Val-43 to Asn-53.		
122	HNHOD46	843488	132	12 - 251	421			
123	HNTBI26	1310821	133	28 - 990	422	Pro-56 to Pro-63, Met-92 to Thr-98, Ser-112 to Pro-120, Pro-162 to Glu-173,		

						Ala-200 to Ser-210, Lys-311 to Asn-320.		
	HNTBI26	796807	251	32 - 547	540	Pro-56 to Pro-63, Met-92 to Thr-98, Ser-112 to Pro-120, Pro-162 to Ser-169.		
	HNTBI26	590738	252	16 - 411	541	Pro-56 to Pro-63, Met-92 to Thr-98, Arg-107 to Pro-120.		
124	HNTBL27	545534	134	100 - 447	423	Arg-45 to Thr-52, Tyr-60 to Gly-66, Ala-87 to Trp-92, Leu-105 to Ser-115.	3p21.31	116806, 168468, 182280, 212138, 600163
125	HNTCE26	1160395	135	111 - 1316	424	Tyr-2 to Gly-15, Trp-192 to Asp-199, Lys-248 to Leu-253, Arg-330 to Lys-336, Gln-354 to Val-364, Val-383 to Ser-392.		
	HNTCE26	853373	253	57 - 422	542	Arg-75 to Lys-81, Gln-99 to Asp-109.		
126	HNTNI01	1352285	136	307 - 534	425	Lys-71 to Trp-76.		
	HNTNI01	699848	254	306 - 455	543			
127	HODDF13	684307	137	46 - 171	426	Thr-28 to Ser-40.		
128	HODDN92	422913	138	434 - 541	427			
129	HOFMQ33	1184465	139	49 - 1503	428	Leu-37 to Gly-44, Thr-137 to Leu-144, Ala-178 to Asn-184, Asp-194 to Val-201, Leu-252 to Glu-258, Asp-280 to Tyr-293, Asn-296 to Thr-301,		

						Asp-322 to Asp-348, Asn-363 to Ser-368, His-370 to Thr-378, Asn-380 to Cys-386, Glu-391 to Cys-399, Leu-421 to Arg-426, Glu-454 to Tyr-459.		
	HOFMQ33	919896	255	48 - 1502	544	Leu-37 to Gly-44, Pro-46 to Gly-51, Thr-137 to Leu-144, Ala-178 to Asn-184, Asp-194 to Val-201, Leu-252 to Glu-258, Asp-280 to Tyr-293, Asn-296 to Thr-301, Asp-322 to Asp-348, Asn-363 to Ser-368, His-370 to Thr-378, Asn-380 to Cys-386, Glu-391 to Cys-399, Leu-421 to Arg-426, Glu-454 to Tyr-459.		
	HOFMQ33	906694	256	78 - 875	545	Leu-37 to Gly-43.		
	HOFMQ33	902639	257	724 - 741	546			
	HOFMQ33	702186	258	123 - 374	547	Met-2 to Ser-9.		
130	HOFOC73	931871	140	18 - 407	429	Pro-22 to Cys-30, Gly-43 to Tyr-53, Ser-55 to Trp-65, Ala-76 to His-81, Pro-101 to Gly-108, Pro-121 to Gly-127.		
	HOFOC73	907073	259	23 - 226	548	Thr-47 to Pro-55.		
	HOFOC73	907072	260	127 - 171	549	Pro-1 to Val-7.		

	HOFOC73	878863	261	142 - 162	550			
131	HOQBJ82	1352356	141	361 - 852	430	Ser-30 to Met-36, Ile-38 to Pro-46, Gln-78 to Gly-88, Thr-98 to Pro-105, Gly-110 to Ser-122, Ser-136 to Trp-144.		
	HOQBJ82	858338	262	102 - 584	551	Ser-30 to Met-36, Ile-38 to Pro-46, Gln-78 to Gly-88, Thr-98 to Pro-105, Gly-110 to Ser-122.		
	HOQBJ82	857453	263	55 - 1029	552			
132	HOSBY40	589431	142	89 - 259	431			
133	HOSDJ25	854234	143	1076 - 1195	432	Gly-18 to Lys-23, Pro-31 to Gly-38.		
	HOSDJ25	566845	264	146 - 268	553	Gly-18 to Lys-23, Pro-31 to Gly-38.		
134	HPEAD79	520202	144	51 - 176	433	Lys-16 to Ser-21, Gly-36 to Asp-41.		
135	HPIBO15	1310868	145	128 - 763	434	Asp-40 to Glu-50, Ser-59 to Gly-69, Leu-109 to Lys-117, Tyr-130 to Leu-137, Leu-140 to Glu-160, Gly-202 to Tyr-208.		
	HPIBO15	590741	265	127 - 648	554	Asp-40 to Glu-50, Ser-59 to Gly-69, Ala-98 to His-105, Arg-108 to Glu-114, Pro-124 to Ser-138, Ala-143 to Gly-154.		

136	HPJBI33	685699	146	236 - 397	435	Arg-30 to Gln-36.		
137	HPJBK12	1011467	147	126 - 272	436		4,8	
	HPJBK12	525375	266	119 - 265	555			
	HPJBK12	796925	267	969 - 1001	556			
	HPJBK12	699587	268	509 - 523	557			
138	HPMDK28	846357	148	64 - 669	437	Ala-55 to Asn-60, Lys-65 to Met-71, Leu-75 to Asn-86, Asp-93 to Asp-110, Leu-130 to Cys-138, Gln-149 to Glu-154, Thr-172 to Ile-179, Glu-185 to Arg-192.	1p36.33	
	HPMDK28	639118	269	58 - 663	558	Ala-55 to Asn-60, Lys-65 to Met-71, Leu-75 to Asn-86, Asp-93 to Asp-110, Leu-130 to Cys-138, Gln-149 to Glu-154, Thr-172 to Ile-179, Glu-185 to Arg-192.		
139	HPRAL78	1352342	149	62 - 1321	438	Pro-31 to Thr-48, Arg-62 to Gly-70, Ala-74 to Glu-87, Lys-123 to Asp-129, Pro-162 to Gly-167, Glu-170 to Gly-189, Arg-220 to Asn-228, Glu-248 to Ala-258, Gly-285 to Gly-300, Pro-315 to Gly-327, Ser-406 to Arg-411.	3p25.2	193300, 193300, 227646

	HPRAL78	844216	270	70 - 1245	559	Pro-31 to Thr-48, Arg-62 to Gly-70, Ala-74 to Glu-87, Lys-123 to Asp-129, Pro-162 to Gly-167, Glu-170 to Gly-189, Arg-220 to Asn-228.		
	HPRAL78	484735	271	148 - 339	560	Ser-49 to Arg-54.		
140	HRABA80	882176	150	144 - 452	439	Ala-30 to Gly-36, Asp-45 to Trp-50, Lys-65 to Cys-71, Pro-80 to Cys-87.		
	HRABA80	588460	272	130 - 438	561	Ala-30 to Gly-36, Asp-45 to Trp-50, Lys-65 to Cys-71, Pro-80 to Cys-87.		
141	HRACD15	871221	151	252 - 410	440			
	HRACD15	706332	273	252 - 413	562			
142	HRACJ35	877666	152	132 - 1550	441	Arg-31 to Lys-37, Lys-58 to Glu-65, Asp-157 to Gly-168, Ile-219 to Gly-225, Ala-260 to Ser-268, Thr-276 to Glu-282.	8q22.2	148900, 216550
	HRACJ35	730504	274	99 - 1517	563	Arg-31 to Lys-37, Lys-58 to Glu-65, Asp-157 to Gly-168, Ile-219 to Gly-225, Ala-260 to Ser-268, Thr-276 to Glu-282.		
	HRACJ35	470546	275	1 - 534	564	Ile-9 to Gly-15, Ala-50 to Ser-58,		

						Thr-66 to Glu-72.		
143	HRGBL78	910133	153	30 - 1109	442	Thr-48 to Arg-56, Pro-122 to Glu-127, Lys-135 to Cys-143, Ala-180 to Gly-185, Ala-230 to Tyr-238, Thr-244 to Gln-255, Pro-274 to Ser-279, Thr-284 to Phe-306, Leu-345 to Thr-354.	1	
	HRGBL78	904040	276	30 - 626	565	Thr-48 to Arg-56, Pro-122 to Glu-127, Ala-136 to Tyr-141.		
	HRGBL78	904621	277	11 - 19	566			
	HRGBL78	863802	278	1048 - 1146	567	Pro-24 to Arg-32.		
144	HROAJ39	1181699	154	10 - 1146	443	Ile-4 to Tyr-10, Arg-119 to Pro-126, Glu-152 to Gly-158, Thr-209 to Phe-215.	18q21.32	174810, 601567, 602080
	HROAJ39	1114849	279	31 - 879	568	Arg-40 to Pro-47, Glu-73 to Gly-79, Thr-130 to Phe-136, Lys-277 to Lys-283.		
	HROAJ39	1027712	280	247 - 1104	569	Arg-40 to Pro-47, Glu-73 to Gly-79, Thr-130 to Phe-136.		
145	HROBD68	827306	155	122 - 268	444	Thr-19 to Thr-25.		
146	HSAWD74	460527	156	142 - 570	445	Leu-51 to Gly-77, Ile-117 to Pro-125.	7	
	HSAWD74	371416	281	122 - 256	570	Thr-25 to Cys-30, Pro-35 to Arg-42.		
147	HSDEK49	1352253	157	60 - 1256	446	Val-29 to Val-37,	Xq12-q13.3	300011, 300011, 300011, 300127, 305450,

						Asp-71 to His-76, Gln-78 to Gly-84, Met-105 to His-110, Trp-117 to Asn-123, Lys-179 to Pro-187, Gly-218 to Asp-224, Leu-237 to Ala-243, Thr-256 to Asp-268, Ser-275 to Lys-280, Arg-308 to Glu-314, Glu-326 to Glu-332, Cys-343 to Asp-359.		309605, 313700, 313700, 313700, 313700, 313700, 314580
	HSDEK49	625998	282	126 - 1043	571	Val-29 to Val-37, Asp-71 to His-76, Gln-78 to Gly-84, Met-105 to His-110, Trp-117 to Gly-122, Gln-136 to Lys-141, Leu-143 to Ala-149, Thr-162 to Asp-174, Ser-181 to Lys-186, Arg-214 to Glu-220, Glu-232 to Glu-238, Cys-249 to Asp-265.		
148	HSDFJ26	834619	158	99 - 767	447	Ala-21 to Glu-31, Thr-37 to Cys-43, Asp-62 to Ser-79, Lys-134 to Gly-146, Leu-164 to Met-169, Glu-171 to Lys-201.		
	HSDFJ26	836071	283	99 - 317	572	Ala-21 to Glu-31, Thr-37 to Cys-43, Pro-64 to Asp-69.		

149	HSDSB09	1301498	159	16 - 423	448	Glu-33 to Glu-56, Thr-75 to Cys-81.		
	HSDSB09	463645	284	22 - 387	573	Glu-33 to Glu-56, Thr-75 to Cys-81.		
150	HSDSE75	545057	160	160 - 705	449	Tyr-15 to Leu-59, Ala-68 to Asp-85, Pro-87 to Asn-96, His-120 to Lys-129, Ser-153 to Gln-170.		
151	HSIDJ81	589447	161	8 - 184	450	Glu-37 to Gly-45.		
152	HSKDA27	1352409	162	786 - 3635	451	Gly-31 to Arg-36, Thr-55 to Glu-62, Ser-64 to Ser-79, Arg-87 to Asp-96, Arg-103 to Ala-109, Asp-120 to Arg-126, Gly-294 to Gly-302, Ser-305 to Ala-318, Val-320 to Arg-327, Pro-344 to Thr-351, Thr-383 to Thr-399, Leu-414 to Lys-435, Thr-449 to Ala-457, Gly-461 to Asn-479, Gly-483 to Gln-498, Ser-503 to Arg-514, Lys-532 to Ala-559, Leu-563 to Ser-611, Lys-632 to Tyr-638, Asn-667 to Lys-672, Leu-701 to Met-707, Ser-745 to Lys-755, Lys-761 to Leu-768,		

						Pro-787 to Trp-792, Lys-871 to Met-883, Pro-914 to Tyr-923, Ser-925 to Arg-939, Glu-942 to Tyr-950.		
	HSKDA27	1074734	285	127 - 1653	574	Gly-31 to Arg-36, Thr-55 to Glu-62, Ser-64 to Ser-79, Arg-87 to Asp-96, Arg-103 to Ala-109, Asp-120 to Arg-126, Gly-294 to Gly-302, Ser-305 to Ala-318, Val-320 to Arg-327, Pro-342 to Thr-351, Thr-383 to Thr-399, Leu-414 to Lys-435, Thr-449 to Ala-457, Gly-461 to Asn-479, Gly-483 to Gln-498, Asn-504 to Val-509.		
	HSKDA27	872570	286	12 - 1673	575	Gly-27 to Arg-32, Thr-51 to Glu-58, Ser-60 to Ser-75, Arg-83 to Asp-92, Arg-99 to Ala-105, Asp-116 to Arg-122, Gly-290 to Ala-314, Val-316 to Arg-323, Pro-338 to Arg-345, Thr-358 to His-375, Arg-403 to Ser-408, Ser-420 to Ser-436,		

						Thr-447 to Ala-455, Gly-459 to Asn-477, Gly-481 to Gln-496, Ser-501 to Arg-512, Lys-530 to Lys-554.		
153	HSKGN81	676075	163	353 - 1132	452	Ile-60 to Asn-69, Leu-106 to Asp-112, Glu-130 to Gly-136, Phe-160 to Glu-167, Pro-184 to Cys-190, Glu-197 to Ser-202, Arg-215 to Glu-221, Thr-237 to Pro-242.	22q13.2	188826
	HSKGN81	409905	287	537 - 608	576	Thr-11 to Pro-22.		
154	HSNAD72	467397	164	220 - 327	453			
155	HSNMC45	1352201	165	225 - 389	454	Glu-23 to Asn-31, Thr-38 to Gly-48.		
	HSNMC45	545060	288	232 - 309	577			
156	HSQFP66	460537	166	96 - 332	455	Ser-6 to Arg-15.		
157	HSRFZ57	892171	167	82 - 207	456			
158	HSUBW09	413246	168	153 - 323	457	Asp-23 to Gly-29.		
159	HSVBU91	596868	169	256 - 528	458	Asp-26 to Asn-31, Ser-37 to His-49, Ala-65 to Ser-73.	7q11.23	116860, 129900, 233700, 600079
160	HTAEE28	1018291	170	319 - 1167	459	Pro-255 to Leu-264.		
	HTAEE28	882919	289	372 - 737	578			
	HTAEE28	864120	290	124 - 771	579			
161	HTECC05	1352365	171	13 - 546	460	Gly-41 to Leu-46, Asp-67 to Thr-75, Ile-114 to Gly-122, Pro-156 to Trp-161.		
	HTECC05	877448	291	21 - 404	580	Gly-41 to Leu-46,		

						Asp-67 to Thr-75, Ile-114 to Pro-127.		
	HTECC05	666743	292	27 - 518	581	Gly-41 to Leu-46, Asp-67 to Thr-75, Ile-114 to Ala-123.		
162	HTEEB42	206980	172	59 - 952	461	Met-1 to His-7.	21q21.2	
163	HTEFU65	543396	173	231 - 371	462	Gly-35 to Gly-40.		
164	HTELP17	836072	174	164 - 298	463		3p12-p11.1	164500, 176880, 232500, 600151, 600795
165	HTELS08	847090	175	15 - 491	464	Pro-98 to Gln-106.		
166	HTLEP53	634852	176	73 - 378	465	Ser-33 to Lys-43.		
167	HTPCS72	854941	177	2365 - 2577	466		1q23.1	107300, 131210, 136132, 145001, 173610, 601652
	HTPCS72	566683	293	530 - 745	582			
168	HTPIH83	919916	178	118 - 810	467	Ser-29 to Ser-34, Ser-186 to Asp-196, Arg-206 to Ser-225.	Xq22.3-23	300046, 300067, 300067, 300121, 300121, 301201, 301835, 311850
	HTPIH83	895024	294	111 - 530	583	Ser-29 to Ser-34.		
	HTPIH83	898088	295	96 - 353	584			
169	HTSEW17	460579	179	170 - 283	468			
170	HTTBI76	637725	180	133 - 534	469	Glu-55 to Arg-61, Gln-84 to Ser-92, Ser-99 to Ser-104.		
171	HTTBS64	1008159	181	95 - 223	470	Leu-37 to Asn-42.		
	HTTBS64	863187	296	100 - 228	585	Leu-37 to Asn-42.		
	HTTBS64	754125	297	175 - 402	586	Lys-41 to Arg-46.		
172	HTXJM03	603918	182	328 - 498	471	Asp-51 to His-56.		
173	HTXON32	838288	183	72 - 230	472	Ala-45 to Gly-50.		
174	HUFCJ30	638402	184	123 - 275	473	Pro-31 to Ala-37.		
175	HUVEB53	571200	185	14 - 151	474		20p12	112261, 176640, 176640, 176640, 236700, 601920
176	HWAAD63	838626	186	322 - 825	475	Pro-53 to Trp-61.		
	HWAAD63	833089	298	322 - 483	587			

	HWAAD63	793875	299	312 - 818	588			
177	HWADJ89	799506	187	581 - 709	476		1p36.31-p36.11	120550, 120570, 120575, 130500, 133200, 600975
178	HWBFX31	799427	188	271 - 426	477			

Table 1B.2

Gene No:	cDNA Clone ID	Contig ID:	SEQ ID NO:X	Tissue Distribution Library Code:Count (see Table 4 for Library Codes)
1	H2CBU83	884134	11	AR182:8, AR314:7, AR271:7, AR280:6, AR315:6, AR216:6, AR052:6, AR224:6, AR225:5, AR164:5, AR215:5, AR270:5, AR165:5, AR162:5, AR310:5, AR245:5, AR166:5, AR161:5, AR169:5, AR223:5, AR266:5, AR172:5, AR039:5, AR192:5, AR163:4, AR193:4, AR207:4, AR176:4, AR269:4, AR175:4, AR226:4, AR243:4, AR217:4, AR273:4, AR168:4, AR282:4, AR204:4, AR291:4, AR265:4, AR183:4, AR274:4, AR299:4, AR214:4, AR205:4, AR206:4, AR194:4, AR060:4, AR272:4, AR238:4, AR186:4, AR222:4, AR053:4, AR197:4, AR089:3, AR257:3, AR295:3, AR289:3, AR311:3, AR221:3, AR171:3, AR191:3, AR250:3, AR235:3, AR252:3, AR275:3, AR309:3, AR177:3, AR180:3, AR173:3, AR178:3, AR246:3, AR312:3, AR188:3, AR292:3, AR298:3, AR284:3, AR212:3, AR201:3, AR285:3, AR189:3, AR296:3, AR181:3, AR300:3, AR185:3, AR253:3, AR202:3, AR281:3, AR237:3, AR184:3, AR268:3, AR233:3, AR286:3, AR232:3, AR308:3, AR277:3, AR267:3, AR228:3, AR288:3, AR316:3, AR239:3, AR195:2, AR242:2, AR263:2, AR033:2, AR287:2, AR196:2, AR210:2, AR259:2, AR174:2, AR294:2, AR096:2, AR234:2, AR293:2, AR290:2, AR190:2, AR255:2, AR055:2, AR213:2, AR264:2, AR231:2, AR313:2, AR297:2, AR258:2, AR170:2, AR218:2, AR247:2, AR061:2, AR236:2, AR219:2, AR198:2, AR230:2, AR254:2, AR256:2, AR261:2, AR104:2, AR240:2, AR262:2, AR283:2, AR229:2, AR227:2, AR260:2, AR200:1, AR203:1, AR179:1, AR244:1, AR199:1 S0414:9, S0422:7, L0662:7, S0444:6, L0748:4, L0581:4, S0442:3, H0031:3, L0666:3, L0754:3, H0656:2, S0358:2, S0360:2, H0013:2, S0438:2, S0440:2, L0598:2, L0803:2, L0540:2, L0756:2, L0752:2, L0758:2, L0759:2, S0242:2, H0624:1, S0282:1, H0742:1, H0393:1, H0586:1, H0574:1, H0036:1, H0004:1, T0103:1, T0110:1, H0571:1, H0569:1, H0123:1, L0471:1, H0594:1, S6028:1, H0622:1, UNKWN:1, L0649:1, L0381:1, L0776:1, L0659:1, L0528:1, L0792:1, L0793:1, L0663:1, L0664:1, L0665:1, L2257:1, H0144:1, S0374:1, H0547:1, H0593:1, H0690:1, H0670:1, H0648:1, H0672:1, H0651:1, H0539:1, S0378:1, S0380:1, H0521:1, S0406:1, H0555:1, H0478:1, L0744:1, L0731:1 and S0276:1.
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2	H6EDC19	543259	12	AR235:21, AR197:20, AR222:17, AR261:13, AR309:11, AR195:11, AR176:9, AR201:9, AR264:9, AR295:9, AR162:9, AR271:9, AR242:9, AR161:9, AR163:9, AR177:9, AR165:9, AR089:9, AR236:8, AR164:8, AR283:8, AR252:8, AR196:8, AR166:8, AR296:8, AR229:8, AR198:8, AR263:7, AR297:7, AR181:7, AR269:7, AR287:7, AR289:7, AR288:7, AR245:7,

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6	HAJAN23	1352364	16	AR192:7, AR169:6, AR207:6, AR170:6, AR168:5, AR214:5, AR161:5, AR162:5, AR165:5, AR172:5, AR163:5, AR223:5, AR311:5, AR195:5, AR164:5, AR166:5, AR196:5, AR224:4, AR222:4, AR171:4, AR217:4, AR264:4, AR308:4, AR216:4, AR277:4, AR282:4, AR271:4, AR291:4, AR213:4, AR197:4, AR193:3, AR235:3, AR309:3, AR212:3, AR205:3, AR283:3, AR250:3, AR253:3, AR261:3, AR225:3, AR188:3, AR089:3, AR245:3, AR316:3, AR312:3, AR299:3, AR215:3, AR177:3, AR055:3, AR247:3, AR268:2, AR295:2, AR288:2, AR221:2, AR313:2, AR199:2, AR262:2, AR033:2, AR230:2, AR285:2, AR039:2, AR297:2, AR229:2, AR198:2, AR300:2, AR257:2, AR286:2, AR287:2, AR104:2, AR274:2, AR060:2, AR173:2, AR246:2, AR272:2, AR096:2, AR227:2, AR232:2, AR237:2, AR176:2, AR182:2, AR226:2, AR185:2, AR238:2, AR266:2, AR181:2, AR240:2, AR231:2, AR211:2, AR258:2, AR289:2, AR191:2, AR239:2, AR175:1, AR189:1, AR270:1, AR219:1, AR234:1, AR061:1, AR183:1, AR200:1, AR263:1, AR203:1, AR228:1, AR236:1, AR296:1, AR201:1, AR210:1 S0408:2, H0619:2, S0438:2, L0803:2, L0804:2, L3643:1, H0686:1, H0650:1, H0730:1, T0110:1, H0233:1, S0003:1, H0674:1, H0623:1, H0561:1, H0509:1, S0422:1, L0770:1, L0766:1, L0518:1, L5622:1, S0374:1, H0593:1, H0555:1, L0748:1 and L0755:1.
	HAJAN23	872551	191	
7	HAJBR69	638516	17	AR309:4, AR242:3, AR217:3, AR235:3, AR225:3, AR170:2, AR252:2, AR263:2, AR180:2, AR171:2, AR282:2, AR221:2, AR197:2, AR200:2, AR196:2, AR308:2, AR277:2, AR165:1, AR164:1, AR215:1, AR192:1, AR166:1, AR268:1, AR168:1, AR211:1, AR207:1, AR283:1, AR216:1, AR204:1, AR311:1, AR240:1, AR182:1 S0040:4, T0010:4, H0560:4, L0794:4, S0420:3, L0455:3, L3905:3, H0656:2, S0212:2, H0619:2, H0497:2, H0052:2, H0012:2, H0429:2, L0766:2, L5623:2, L0439:2, H0665:2, H0556:1, H0717:1, H0650:1, S0418:1, H0580:1, H0728:1, H0735:1, H0734:1, H0370:1, H0392:1, H0333:1, H0013:1, H0635:1, H0505:1, H0581:1, H0569:1, H0050:1, H0373:1, S0250:1, S0022:1, H0553:1, L0370:1, H0561:1, L2263:1 L2261:1, H0520:1, H0593:1, S0126:1, H0435:1, H0518:1, H0521:1, H0626:1, L0748:1, S0436:1, L0591:1, H0542:1, S0424:1 and H0677:1.
8	HAMFE15	905695	18	AR235:3, AR275:3, AR221:3, AR282:2, AR207:2, AR291:2, AR180:2, AR286:2, AR173:2, AR178:2, AR225:2, AR243:2, AR272:1, AR176:1, AR181:1, AR163:1, AR161:1, AR285:1, AR168:1, AR257:1, AR277:1, AR261:1, AR191:1, AR311:1, AR196:1, AR216:1, AR296:1, AR297:1, AR269:1, AR169:1, AR266:1, AR247:1, AR199:1, AR175:1 L0748:10, L0754:9, L0731:9, L0766:8, L0439:7, L0803:6, H0624:5, L0759:5, S0356:4, H0486:4, H0090:4, L0789:4, L0438:4, L0740:4, L0749:4,

				L0756:4, L0777:4, L0599:4, S0360:3, H0013:3, S0003:3, L0369:3, L0794:3, L0659:3, L0809:3, L0665:3, H0539:3, L0362:3, S0114:2, S0358:2, S0278:2, H0441:2, H0586:2, H0333:2, H0581:2, H0328:2, H0553:2, H0529:2, L0770:2, L0662:2, L0804:2, L0666:2, L0663:2, H0547:2, H0519:2, H0659:2, H0670:2, S0330:2, L0747:2, L0750:2, L0755:2, L0758:2, L0589:2, L0592:2, L0581:2, L0593:2, S0276:2, S0424:2, H0170:1, H0171:1, S0040:1, S0116:1, H0664:1, H0458:1, H0638:1, H0192:1, S0418:1, S0354:1, S0410:1, H0580:1, S0046:1, H0393:1, L0717:1, H0411:1, S6022:1, S0222:1, H0587:1, T0114:1, L0021:1, H0318:1, H0421:1, H0052:1, H0251:1, H0544:1, H0572:1, H0566:1, L0471:1, H0057:1, H0051:1, H0510:1, S6028:1, H0271:1, S0334:1, H0622:1, S0368:1, H0031:1, L0142:1, H0032:1, H0124:1, H0316:1, H0591:1, H0616:1, L0060:1, H0551:1, H0264:1, H0412:1, H0413:1, L0564:1, H0560:1, S0150:1, H0646:1, S0144:1, H0538:1, L0598:1, L0638:1, L0372:1, L0764:1, L0771:1, L0521:1, L0650:1, L0805:1, L0655:1, L0656:1, L0664:1, H0144:1, S0374:1, H0691:1, H0520:1, H0689:1, H0658:1, H0672:1, S0152:1, S0332:1, H0521:1, H0134:1, H0631:1, S0206:1, L0751:1, L0779:1, L0753:1, H0445:1, S0394:1, L0608:1, S0026:1, H0653:1, H0665:1, S0242:1, S0194:1, H0542:1, H0423:1 and H0422:1.
	HAMFE15	823350	192	
9	HAMGR28	892971	19	AR271:8, AR184:7, AR060:7, AR240:6, AR089:6, AR219:5, AR104:5, AR183:5, AR282:5, AR052:5, AR275:5, AR266:5, AR316:5, AR274:5, AR249:5, AR192:4, AR053:4, AR267:4, AR096:4, AR247:4, AR277:4, AR309:4, AR312:4, AR283:4, AR248:4, AR253:4, AR186:4, AR182:4, AR185:4, AR238:4, AR299:4, AR310:3, AR289:3, AR285:3, AR313:3, AR213:3, AR218:3, AR291:3, AR241:3, AR039:3, AR251:3, AR286:3, AR033:3, AR256:3, AR061:3, AR292:3, AR234:3, AR258:3, AR202:3, AR231:3, AR268:3, AR295:3, AR294:3, AR293:3, AR300:3, AR055:3, AR243:3, AR315:3, AR198:2, AR296:2, AR270:2, AR284:2, AR259:2, AR298:2, AR290:2, AR226:2, AR237:2, AR233:2, AR273:2, AR269:2, AR229:2, AR206:2, AR232:2, AR227:1, AR314:1, AR179:1, AR175:1 L0666:11, H0046:9, H0556:5, L0809:5, L0747:4, L0770:3, L0769:3, L0783:3, H0520:3, L0439:3, L0731:3, H0664:2, S0045:2, H0123:2, H0424:2, L0637:2, L0775:2, S0328:2, S0146:2, L0777:2, L0601:2, H0542:2, L0411:1, H0265:1, H0740:1, H0294:1, H0583:1, H0650:1, H0662:1, S0420:1, S0444:1, H0637:1, H0735:1, S0476:1, S0278:1, H0370:1, H0586:1, H0587:1, H0497:1, H0486:1, H0013:1, H0069:1, H0575:1, H0253:1, H0581:1, H0251:1, H0150:1, T0010:1, H0083:1, H0239:1, H0594:1, H0288:1, H0290:1, H0604:1, H0553:1, H0040:1, H0087:1, H0494:1, H0560:1, L0065:1, S0438:1, S0440:1, H0641:1, H0633:1, H0646:1, L3815:1, S0422:1, S0002:1, H0529:1, L0763:1, L0646:1, L0800:1, L0764:1, L0767:1, L0649:1, L0803:1, L0806:1, L0653:1, L0659:1, L0518:1, L0789:1, L0791:1, S0053:1, H0144:1, H0701:1, H0725:1, S0148:1, L0438:1, H0519:1, H0593:1, S0406:1, L0748:1, L0745:1, L0749:1, L0750:1, L0779:1, L0752:1, L0758:1, S0031:1, S0436:1, S0460:1 and L0600:1.
	HAMGR28	748223	193	
10	HAPOM49	769555	20	AR089:5, AR169:5, AR060:5, AR282:4, AR283:4, AR055:3, AR218:3, AR096:3, AR171:3, AR104:3, AR277:3, AR313:3, AR217:3, AR039:2, AR240:2, AR316:2, AR221:2, AR163:2, AR180:2, AR183:2, AR170:2, AR172:2, AR165:2, AR299:2, AR166:2, AR242:2, AR195:2, AR168:2, AR300:2, AR275:2, AR162:2, AR164:1, AR216:1, AR193:1, AR205:1, AR264:1, AR185:1, AR173:1, AR266:1, AR161:1, AR272:1, AR214:1, AR257:1, AR196:1, AR270:1, AR268:1, AR289:1, AR245:1, AR312:1, AR223:1, AR212:1, AR261:1, AR219:1, AR297:1, AR192:1 S0406:5, L0750:5, L0777:4, L0749:3, L0779:3, H0662:2, S0440:2, L0770:2, L0794:2, L0776:2, L0657:2, L0783:2, L0740:2, L0747:2, L0780:2, S0420:1, S0442:1, S0444:1, S0045:1, L3316:1, H0599:1, H0575:1, S0474:1, T0115:1, H0083:1, H0510:1, H0644:1, H0551:1, S0386:1, H0494:1, H0561:1, H0538:1, S0422:1, L0646:1, L0804:1, L0774:1, L0809:1, L0530:1, L0663:1, L0664:1, L0665:1, H0593:1, S0380:1, S0027:1,

				L0748:1, L0439:1, L0756:1, L0755:1, L0758:1, L0485:1, H0542:1 and H0423:1.
	HAPOM49	722386	194	
11	HATBR65	635514	21	AR313:46, AR173:29, AR258:29, AR096:29, AR229:29, AR300:26, AR218:26, AR240:26, AR247:26, AR214:26, AR196:24, AR223:23, AR175:23, AR257:22, AR174:22, AR178:22, AR165:21, AR217:21, AR162:21, AR183:21, AR161:21, AR089:21, AR293:20, AR163:20, AR264:20, AR164:20, AR033:20, AR309:20, AR216:19, AR181:19, AR262:19, AR166:19, AR185:19, AR299:19, AR180:18, AR312:18, AR179:18, AR238:18, AR290:18, AR297:18, AR189:18, AR188:18, AR269:17, AR270:17, AR199:17, AR294:17, AR261:16, AR224:16, AR191:16, AR316:16, AR285:16, AR225:16, AR203:16, AR235:15, AR182:15, AR263:15, AR219:15, AR177:15, AR212:15, AR274:14, AR236:14, AR226:14, AR234:14, AR053:14, AR231:14, AR287:14, AR233:14, AR296:14, AR275:14, AR176:14, AR193:14, AR171:13, AR286:13, AR282:13, AR267:13, AR255:13, AR210:13, AR268:13, AR308:13, AR190:13, AR060:13, AR291:13, AR222:13, AR260:13, AR200:12, AR104:12, AR211:12, AR237:12, AR295:11, AR266:11, AR252:11, AR213:11, AR168:11, AR288:11, AR254:11, AR215:11, AR228:11, AR221:10, AR272:10, AR230:10, AR250:10, AR204:10, AR039:10, AR242:10, AR239:9, AR245:9, AR289:9, AR195:9, AR256:9, AR170:9, AR169:9, AR172:9, AR283:9, AR246:8, AR205:8, AR227:8, AR198:8, AR277:8, AR271:8, AR311:8, AR192:8, AR197:8, AR243:7, AR253:7, AR201:7, AR232:6, AR207:6, AR061:5, AR055:5 L0534:4, L0562:3, L0527:3, H0254:2, S0045:2, H0156:2, L0589:2, H0255:1, H0402:1, L0539:1, T0060:1, H0328:1, H0615:1, H0598:1, H0264:1, L0766:1, L0493:1, L0666:1, S0052:1, H0539:1, L0747:1, L0752:1 and L0366:1.
12	HAUAI83	639009	22	H0294:2
	HAUAI83	383592	195	
13	HBAMB15	671835	23	AR245:4, AR213:3, AR176:3, AR224:3, AR252:3, AR168:3, AR165:2, AR164:2, AR183:2, AR197:2, AR204:2, AR238:2, AR266:2, AR282:2, AR162:2, AR171:2, AR271:2, AR289:2, AR270:2, AR291:2, AR205:2, AR274:2, AR096:2, AR268:2, AR297:2, AR296:2, AR225:2, AR161:1, AR311:1, AR192:1, AR269:1, AR261:1, AR179:1, AR182:1, AR234:1, AR191:1, AR277:1, AR181:1, AR237:1, AR313:1, AR300:1, AR089:1 H0410:1, H0530:1, H0328:1, L0455:1 and L0740:1.
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				S0360:3, H0052:3, H0545:3, H0038:3, L0766:3, S0380:3, L0740:3, L0751:3, L0757:3, H0653:3, S0358:2, H0733:2, L0717:2, S0278:2, H0318:2, H0309:2, H0327:2, H0150:2, H0687:2, H0181:2, H0413:2, H0509:2, L0769:2, L0764:2, L0771:2, L0662:2, L0768:2, L0774:2, L0776:2, L5622:2, L0666:2, L0663:2, L2261:2, S0126:2, H0658:2, S0406:2, L0744:2, L0758:2, L0588:2, L3643:1, S0342:1, H0713:1, H0740:1, T0049:1, H0657:1, S0116:1, S0282:1, H0255:1, H0402:1, H0638:1, S0418:1, S0420:1, S0442:1, S0444:1, S0408:1, H0730:1, H0741:1, H0735:1, H0776:1, S0300:1, L3388:1, H0370:1, H0592:1, H0643:1, L0623:1, H0156:1, L0021:1, H0253:1, H0263:1, L0738:1, H0530:1, H0571:1, H0081:1, H0578:1, H0083:1, H0266:1, H0039:1, H0604:1, H0031:1, H0616:1, H0087:1, T0004:1, H0494:1, S0438:1, S0142:1, H0743:1, H0529:1, L0763:1, L0796:1, L0761:1, L0645:1, L0773:1, L0364:1, L0561:1, L0650:1, L0651:1, L0653:1, L0655:1, L0661:1, L0629:1, L0657:1, L0658:1, L4669:1, L2258:1, H0725:1, H0519:1, H0670:1, H0672:1, H0518:1, S0044:1, H0555:1, H0436:1, S3014:1, L0439:1, L0749:1, L0731:1, L0759:1, S0260:1, H0445:1, S0434:1, S0196:1, H0423:1 and H0506:1.
	HBGBA69	709658	196	
15	HBIAE26	514418	25	AR161:11, AR162:11, AR163:11, AR313:9, AR242:8, AR165:8, AR039:7, AR164:7, AR166:7, AR207:6, AR201:6, AR204:6, AR089:6, AR096:6, AR197:6, AR309:6, AR053:5, AR193:5, AR264:5, AR299:5, AR060:5, AR182:5, AR173:5, AR185:5, AR198:5, AR236:5, AR300:5, AR181:5, AR228:5, AR271:5, AR176:5, AR277:5, AR055:5, AR262:5, AR196:5, AR247:5, AR250:4, AR258:4, AR312:4, AR257:4, AR175:4, AR229:4, AR178:4, AR179:4, AR316:4, AR293:4, AR269:4, AR274:4, AR240:4, AR261:4, AR246:4, AR104:4, AR266:4, AR177:4, AR191:4, AR233:4, AR275:4, AR192:4, AR268:4, AR183:4, AR213:4, AR205:4, AR231:4, AR297:4, AR288:4, AR174:3, AR212:3, AR294:3, AR270:3, AR267:3, AR238:3, AR180:3, AR215:3, AR255:3, AR245:3, AR199:3, AR287:3, AR226:3, AR296:3, AR234:3, AR203:3, AR218:3, AR285:3, AR282:3, AR311:3, AR195:3, AR200:3, AR239:3, AR283:3, AR263:3, AR217:3, AR222:3, AR272:3, AR291:3, AR237:3, AR033:3, AR290:3, AR188:3, AR243:3, AR253:3, AR189:3, AR225:3, AR295:3, AR230:3, AR170:3, AR061:2, AR219:2, AR286:2, AR308:2, AR227:2, AR256:2, AR232:2, AR216:2, AR190:2, AR171:2, AR289:2, AR211:2, AR223:2, AR235:1, AR214:1 S0049:1 and S0146:1.
16	HBINS58	1352386	26	AR222:31, AR214:31, AR169:26, AR223:23, AR235:22, AR224:22, AR283:21, AR195:20, AR170:20, AR168:20, AR264:20, AR263:19, AR212:19, AR207:18, AR282:18, AR161:18, AR315:18, AR311:18, AR172:17, AR089:17, AR162:16, AR216:16, AR217:16, AR316:16, AR261:16, AR281:16, AR171:16, AR163:16, AR277:16, AR236:14, AR104:14, AR309:14, AR213:13, AR308:13, AR096:13, AR314:13, AR240:13, AR055:12, AR310:12, AR299:12, AR194:12, AR265:12, AR053:12, AR313:12, AR242:12, AR272:12, AR288:12, AR225:11, AR205:11, AR202:11, AR295:11, AR280:11, AR198:11, AR245:11, AR165:11, AR039:11, AR166:11, AR060:11, AR193:10, AR297:10, AR271:10, AR164:10, AR252:10, AR232:10, AR192:10, AR284:10, AR300:10, AR177:10, AR218:10, AR285:10, AR312:9, AR033:9, AR197:9, AR246:9, AR289:9, AR196:9, AR201:9, AR206:9, AR174:9, AR219:9, AR296:9, AR221:9, AR254:9, AR262:9, AR181:8, AR204:8, AR291:8, AR275:8, AR185:8, AR243:8, AR274:8, AR286:8, AR247:8, AR241:8, AR238:8, AR266:8, AR287:7, AR229:7, AR292:7, AR230:7, AR268:7, AR251:7, AR211:7, AR239:7, AR178:7, AR270:7, AR231:7, AR226:7, AR227:7, AR183:7, AR184:7, AR215:6, AR293:6, AR234:6, AR269:6, AR253:6, AR199:6, AR176:6, AR210:6, AR180:6, AR200:6, AR298:6, AR188:6, AR250:6, AR257:6, AR233:5, AR294:5, AR175:5, AR203:5, AR267:5, AR249:5, AR191:5, AR189:5, AR248:5, AR182:5, AR290:5, AR273:5, AR173:5, AR228:5, AR259:5, AR258:5, AR255:5, AR237:5, AR052:5, AR190:5, AR061:4, AR179:4, AR256:4, AR186:3, AR260:3, AR244:3 H0593:2, H0617:1, L0657:1 and L0592:1.

	HBINS58	961712	197	
	HBINS58	892924	198	
17	HBNAW17	526797	27	AR266:6, AR245:3, AR168:2, AR246:2, AR217:2, AR177:2, AR291:2, AR264:2, AR274:1, AR165:1, AR267:1, AR312:1, AR216:1, AR311:1, AR164:1, AR261:1, AR182:1, AR299:1, AR257:1, AR166:1, AR243:1, AR309:1, AR089:1, AR224:1, AR175:1 L0766:3 and H0188:1.
18	HCE2F54	634016	28	AR253:23, AR250:22, AR271:21, AR197:20, AR195:19, AR199:18, AR252:16, AR272:13, AR254:12, AR198:12, AR269:12, AR211:12, AR205:11, AR180:11, AR176:11, AR210:11, AR200:11, AR240:10, AR161:10, AR266:10, AR162:10, AR229:10, AR177:10, AR163:10, AR242:10, AR243:10, AR212:10, AR309:10, AR246:10, AR268:9, AR181:9, AR245:9, AR165:9, AR183:9, AR275:9, AR238:9, AR291:9, AR178:9, AR264:9, AR164:9, AR196:9, AR204:9, AR188:8, AR166:8, AR182:8, AR191:8, AR255:8, AR175:8, AR289:8, AR179:8, AR290:8, AR237:8, AR189:8, AR225:8, AR235:8, AR193:8, AR247:8, AR270:8, AR234:7, AR219:7, AR201:7, AR263:7, AR207:7, AR228:7, AR267:7, AR312:7, AR190:7, AR308:7, AR173:7, AR296:7, AR274:7, AR257:7, AR297:7, AR311:7, AR231:7, AR213:7, AR293:7, AR313:7, AR287:6, AR033:6, AR262:6, AR300:6, AR224:6, AR218:6, AR288:6, AR192:6, AR295:6, AR294:6, AR203:6, AR285:6, AR239:6, AR089:6, AR282:6, AR174:6, AR185:5, AR233:5, AR236:5, AR316:5, AR096:5, AR230:5, AR286:5, AR217:5, AR222:5, AR261:5, AR053:5, AR061:5, AR221:5, AR214:5, AR168:4, AR223:4, AR172:4, AR226:4, AR169:4, AR258:4, AR039:4, AR299:4, AR283:4, AR216:4, AR232:4, AR060:4, AR227:4, AR277:3, AR104:3, AR256:3, AR055:3, AR260:3, AR171:2, AR170:2, AR215:1 H0052:9, L0794:6, L0758:6, L0659:5, L0666:4, L0438:4, S0126:4, L0754:4, L0779:4, H0617:3, L0748:3, L0751:3, L0759:3, H0333:2, H0013:2, H0150:2, H0494:2, L0761:2, L0641:2, L0649:2, L0809:2, L0519:2, L0663:2, S0380:2, L3832:2, L0439:2, L0747:2, L0749:2, H0685:1, H0713:1, H0295:1, H0341:1, H0484:1, H0255:1, H0638:1, S0358:1, S0046:1, S0476:1, H0393:1, L3388:1, H0261:1, S0222:1, H0592:1, H0069:1, H0253:1, H0596:1, H0009:1, H0178:1, H0081:1, H0051:1, H0266:1, H0428:1, H0100:1, S0112:1, L0639:1, L5575:1, L3905:1, L0662:1, L0766:1, L0804:1, L0651:1, L0655:1, L0787:1, L0664:1, L0665:1, T0068:1, H0672:1, H0539:1, L0602:1, S0406:1, H0436:1, H0478:1, L0777:1, L0755:1, H0422:1 and H0506:1.
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	HCE3G69	494346	199	
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21	HCEFB80	1143407	31	H0052:6, L0439:5, L0794:3, L0748:3, L0415:2, H0661:2, H0559:2, S0049:2, H0327:2, S0051:2, H0399:2, S0036:2, L0351:2, L0770:2, H0144:2, L0758:2, L0759:2, S0116:1, S0110:1, H0637:1, H0261:1, S0222:1, H0438:1, H0013:1, H0569:1, H0320:1, S0422:1, H0529:1, L0638:1, L0517:1, L0438:1, S0126:1, L0749:1, L0756:1 and L0592:1.
	HCEFB80	1046853	200	
22	HCEWE20	543370	32	AR253:8, AR053:6, AR196:6, AR198:5, AR191:5, AR313:5, AR245:4, AR181:4, AR174:4, AR195:4, AR189:3, AR096:3, AR089:3, AR213:3, AR177:3, AR270:3, AR254:3, AR300:3, AR190:3, AR269:3, AR224:3, AR247:3, AR188:2, AR275:2, AR175:2, AR226:2, AR165:2, AR171:2, AR312:2, AR179:2, AR162:2, AR180:2, AR164:2, AR299:2, AR161:2, AR163:2, AR257:2, AR238:2, AR166:2, AR240:2, AR185:2, AR268:2, AR207:2, AR223:2, AR199:2, AR060:2, AR178:2, AR316:2, AR204:2, AR173:2, AR295:2, AR200:2, AR183:2, AR212:2, AR309:2, AR233:2, AR216:2, AR229:1, AR294:1, AR237:1, AR290:1, AR235:1, AR239:1, AR228:1, AR288:1, AR234:1, AR201:1, AR168:1, AR289:1, AR293:1, AR286:1, AR222:1, AR236:1, AR258:1, AR182:1, AR033:1, AR287:1, AR283:1, AR282:1, AR266:1, AR232:1, AR262:1, AR230:1 H0052:2, H0261:1, H0271:1 and S0458:1.
23	HCGMD59	636078	33	AR214:5, AR216:4, AR215:4, AR269:4, AR217:3, AR232:3, AR193:3, AR297:3, AR286:3, AR245:3, AR176:3, AR294:3,

				AR264:3, AR197:3, AR295:3, AR200:2, AR312:2, AR096:2, AR165:2, AR104:2, AR263:2, AR183:2, AR164:2, AR243:2, AR168:2, AR195:2, AR238:2, AR277:2, AR283:2, AR033:1, AR171:1, AR296:1, AR060:1, AR228:1, AR172:1, AR210:1, AR227:1, AR224:1, AR061:1, AR289:1, AR309:1, AR237:1, AR308:1, AR293:1 L0748:6, L0750:4, S0386:3, L0439:3, L0777:3, H0624:2, H0052:2, L0435:2, L0598:2, L0809:2, L0751:2, L0747:2, L0756:2, L0753:2, L0731:2, H0422:2, L0718:2, H0265:1, H0381:1, H0459:1, S0356:1, S0360:1, H0619:1, H0393:1, H0411:1, H0050:1, L0455:1, H0412:1, S0344:1, L0769:1, L0638:1, L0764:1, L0771:1, L0803:1, L0804:1, L0805:1, L0776:1, L0438:1, H0689:1, H0659:1, H0658:1, H0660:1, H0666:1, L0594:1 and S0106:1.
24	HCNDR47	1016919	34	AR282:5, AR060:5, AR309:4, AR055:4, AR266:4, AR162:4, AR213:4, AR161:4, AR163:4, AR225:4, AR254:3, AR270:3, AR177:3, AR207:3, AR300:3, AR176:3, AR089:3, AR192:3, AR263:2, AR221:2, AR172:2, AR198:2, AR104:2, AR224:2, AR283:2, AR240:2, AR277:2, AR185:2, AR165:2, AR218:2, AR164:2, AR197:2, AR166:2, AR096:2, AR299:2, AR275:2, AR269:2, AR236:2, AR168:2, AR316:2, AR288:2, AR313:2, AR171:2, AR217:2, AR183:2, AR308:2, AR257:2, AR039:2, AR296:2, AR272:2, AR264:1, AR033:1, AR261:1, AR311:1, AR246:1, AR212:1, AR286:1, AR289:1, AR255:1, AR231:1, AR237:1, AR061:1, AR179:1, AR238:1, AR297:1, AR245:1, AR195:1, AR215:1 L0794:3, L0764:2, L0439:2, H0052:1, H0597:1, T0006:1, L0766:1, H0648:1, S0330:1 and L0753:1.
	HCNDR47	863677	201	
	HCNDR47	874128	202	
25	HCNSM70	637547	35	AR207:46, AR223:40, AR281:39, AR194:39, AR214:36, AR169:35, AR222:34, AR206:34, AR202:33, AR264:32, AR263:30, AR195:30, AR315:29, AR308:29, AR235:28, AR212:28, AR172:28, AR170:27, AR224:27, AR246:27, AR168:27, AR311:26, AR171:26, AR244:25, AR205:25, AR165:25, AR280:24, AR198:24, AR164:24, AR216:23, AR192:23, AR166:23, AR241:23, AR213:23, AR271:22, AR162:22, AR314:22, AR245:22, AR163:21, AR261:21, AR197:21, AR265:21, AR161:20, AR217:20, AR215:20, AR225:19, AR243:19, AR309:19, AR053:19, AR310:18, AR221:18, AR033:18, AR295:17, AR236:17, AR273:17, AR204:17, AR242:17, AR274:16, AR196:16, AR201:15, AR240:15, AR288:15, AR052:15, AR252:15, AR282:15, AR193:14, AR177:14, AR312:14, AR251:14, AR174:14, AR275:13, AR247:13, AR211:13, AR089:13, AR181:13, AR297:13, AR210:12, AR039:12, AR277:12, AR284:12, AR299:12, AR188:12, AR232:12, AR283:12, AR300:12, AR266:12, AR272:12, AR096:12, AR176:12, AR289:11, AR180:11, AR229:11, AR199:11, AR238:11, AR313:11, AR291:11, AR285:11, AR191:11, AR178:11, AR262:11, AR292:10, AR186:10, AR316:10, AR239:10, AR226:10, AR230:10, AR173:10, AR231:10, AR250:9, AR227:9, AR055:9, AR286:9, AR219:9, AR293:9, AR185:9, AR296:9, AR255:9, AR104:9, AR175:9, AR200:9, AR258:9, AR298:9, AR253:9, AR237:9, AR218:9, AR190:9, AR287:9, AR183:8, AR268:8, AR203:8, AR260:8, AR234:8, AR257:8, AR179:8, AR189:8, AR254:8, AR269:8, AR270:8, AR182:8, AR061:8, AR256:7, AR248:7, AR233:7, AR060:7, AR294:7, AR228:7, AR259:6, AR290:6, AR267:6, AR249:5, AR184:5 L0748:5, H0046:2, H0012:2, H0620:2, L0804:2, L0747:2, H0624:1, H0662:1, S0356:1, S0358:1, H0602:1, H0592:1, H0013:1, H0042:1, T0110:1, H0231:1, H0622:1, H0264:1, H0494:1, L0771:1 L0666:1, S0374:1, H0693:1, H0593:1, H0670:1, H0672:1, L0749:1, L0779:1, L0758:1, L0596:1 and H0506:1.
	HCNSM70	589445	203	
26	HCUIM65	550208	36	AR223:4, AR215:3, AR268:3, AR270:3, AR250:3, AR161:3, AR246:3, AR162:3, AR166:2, AR171:2, AR254:2, AR217:2, AR213:2, AR177:2, AR089:2, AR243:2, AR290:2, AR257:2, AR269:2, AR288:1, AR313:1, AR179:1, AR205:1, AR309:1, AR165:1, AR163:1, AR170:1, AR261:1, AR225:1, AR195:1, AR240:1, AR181:1, AR238:1, AR193:1, AR299:1 L0789:4,

				L0809:2, L0759:2, L0596:2, H0306:1, H0402:1, H0580:1, H0550:1, H0370:1, H0404:1, H0559:1, H0486:1, H0031:1, H0674:1, H0135:1, H0100:1, L0800:1, L0794:1, L0804:1, L0805:1, L0515:1, L0783:1, H0672:1, L0777:1, H0444:1 and H0352:1.
27	HCWDS72	707833	37	AR194:5, AR162:5, AR241:4, AR215:4, AR249:4, AR313:3, AR221:3, AR207:3, AR310:3, AR169:3, AR265:3, AR229:3, AR183:3, AR298:2, AR282:2, AR284:2, AR291:2, AR292:2, AR270:2, AR312:2, AR223:2, AR165:2, AR273:2, AR182:2, AR164:2, AR227:2, AR240:2, AR289:2, AR166:2, AR172:2, AR266:2, AR246:2, AR061:2, AR222:2, AR293:2, AR269:2, AR053:2, AR171:2, AR238:2, AR295:2, AR271:1, AR177:1, AR163:1, AR299:1, AR052:1, AR290:1, AR039:1, AR231:1, AR296:1, AR096:1, AR178:1, AR186:1, AR232:1, AR294:1, AR285:1, AR286:1, AR192:1, AR233:1, AR268:1, AR247:1, AR161:1, AR230:1, AR274:1, AR226:1, AR210:1, AR300:1, AR089:1, AR311:1, AR277:1, AR234:1, AR237:1, AR193:1, AR206:1, AR259:1, AR201:1, AR168:1, AR216:1 L0752:30, L0754:17, L0740:16, H0521:14, L0439:14, L0766:12, S0003:11, S0214:11, L0777:10, S0002:8, L0770:8, L0776:8, L0748:8, L0755:8, S0360:7, L0665:7, L0757:7, T0067:6, S0440:6, L0666:6, L0747:6, L0774:5, L0751:5, S0222:4, H0575:4, H0622:4, L0662:4, L0775:4, H0547:4, S0126:4, S0380:4, L0750:4, L0758:4, S0436:4, L0362:4, H0638:3, H0580:3, H0494:3, S0422:3, L0598:3, S0374:3, H0710:3, H0522:3, H0555:3, L0356:3, L0756:3, L0780:3, L0731:3, L0759:3, L0594:3, S0134:2, S0376:2, S0046:2, H0393:2, S0278:2, H0438:2, H0586:2, L2477:2, H0156:2, S0474:2, H0581:2, H0421:2, T0110:2, L0471:2, S6028:2, S0022:2, H0090:2, H0591:2, H0040:2, H0551:2, H0412:2, L0520:2, L0764:2, L0768:2, L0803:2, L0655:2, L0807:2, L0659:2, L0664:2, L0438:2, H0648:2, H0672:2, S0406:2, S0028:2, L0588:2, L0599:2, H0667:2, S0196:2, H0624:1, H0171:1, H0265:1, S0040:1, H0713:1, S0114:1, L0811:1, H0341:1, S0212:1, S0001:1, H0661:1, H0305:1, S0418:1, L3649:1, H0741:1, S0045:1, H0747:1, S0132:1, S0476:1, L3089:1, H0619:1, H0415:1, H0409:1, L1942:1, L2495:1, L3655:1, H0013:1, S0010:1, S0665:1, H0327:1, H0046:1, L0157:1, S0051:1, T0010:1, H0266:1, H0179:1, H0615:1, H0096:1, H0031:1, H0553:1, L0055:1, H0674:1, H0163:1, H0038:1, H0264:1, H0413:1, L0564:1, H0560:1, H0359:1, H0509:1, S0142:1, S0344:1, UNKWN:1, L0369:1, L0762:1, L0371:1, L0796:1, L0761:1, L0373:1, L0773:1, L0521:1, L0794:1, L0804:1, L0784:1, L0518:1, L0783:1, L0647:1, L5622:1, L5623:1, L3391:1, L2657:1, L2262:1, L3636:1, H0144:1, H0684:1, H0659:1, H0658:1, S0330:1, S0152:1, H0696:1, S0404:1, S0037:1, L0746:1, L0779:1, S0031:1, H0707:1, S0434:1, L0480:1, L0608:1, L0604:1, S0011:1, S0192:1, S0456:1 and H0506:1.
28	HCWKC15	553621	38	AR313:9, AR164:8, AR165:8, AR166:8, AR163:7, AR161:7, AR162:7, AR089:6, AR039:5, AR173:5, AR096:5, AR180:5, AR192:4, AR263:4, AR299:4, AR282:4, AR242:4, AR053:4, AR178:4, AR175:4, AR247:4, AR269:4, AR296:4, AR257:3, AR212:3, AR174:3, AR240:3, AR262:3, AR196:3, AR274:3, AR312:3, AR234:3, AR229:3, AR199:3, AR243:3, AR264:3, AR185:3, AR300:3, AR179:3, AR311:3, AR191:3, AR293:3, AR181:3, AR272:3, AR297:3, AR213:3, AR171:3, AR270:3, AR183:3, AR238:3, AR236:3, AR316:3, AR060:3, AR308:3, AR294:3, AR266:3, AR226:3, AR177:3, AR258:3, AR285:2, AR104:2, AR233:2, AR172:2, AR193:2, AR197:2, AR291:2, AR231:2, AR188:2, AR219:2, AR255:2, AR275:2, AR189:2, AR237:2, AR290:2, AR295:2, AR287:2, AR277:2, AR218:2, AR267:2, AR182:2, AR228:2, AR268:2, AR204:2, AR190:2, AR246:2, AR239:2, AR232:2, AR261:2, AR223:2, AR201:2, AR217:2, AR195:2, AR260:1, AR200:1, AR170:1, AR286:1, AR216:1, AR288:1, AR222:1, AR227:1, AR230:1 H0305:2 and H0589:1.
29	HDHEB60	499233	39	AR195:10, AR245:9, AR242:9, AR309:9, AR196:8, AR192:8, AR225:8, AR198:8, AR207:8, AR246:8, AR169:8, AR170:8, AR223:8, AR224:7, AR214:7, AR039:7, AR172:7, AR215:7, AR201:7, AR222:7, AR193:7, AR205:7, AR221:7, AR199:7, AR272:7, AR168:7, AR089:7, AR213:6, AR263:6, AR165:6, AR216:6, AR164:6, AR274:6, AR217:6, AR261:6, AR053:6,

				AR166:6, AR055:6, AR312:6, AR308:6, AR197:6, AR283:5, AR240:5, AR282:5, AR171:5, AR253:5, AR235:5, AR311:5, AR295:5, AR250:5, AR275:5, AR243:5, AR291:5, AR162:5, AR297:5, AR264:5, AR313:5, AR288:5, AR316:5, AR204:5, AR163:5, AR299:5, AR161:5, AR257:5, AR286:5, AR271:5, AR189:5, AR236:5, AR210:5, AR177:5, AR060:4, AR212:4, AR033:4, AR285:4, AR188:4, AR200:4, AR174:4, AR287:4, AR096:4, AR296:4, AR258:4, AR175:4, AR218:4, AR176:4, AR293:4, AR180:4, AR191:4, AR203:4, AR219:4, AR289:4, AR277:4, AR256:4, AR183:4, AR190:4, AR247:4, AR300:4, AR181:3, AR269:3, AR173:3, AR262:3, AR238:3, AR268:3, AR178:3, AR185:3, AR255:3, AR270:3, AR294:3, AR266:3, AR211:3, AR260:3, AR229:3, AR104:3, AR231:3, AR267:3, AR239:3, AR290:3, AR182:3, AR226:3, AR232:3, AR061:2, AR233:2, AR237:2, AR227:2, AR234:2, AR179:2, AR230:2, AR228:2 H0265:2, S0442:2, S0360:2, H0581:2, H0052:2, H0570:2, H0087:2, L0439:2, H0445:2, H0650:1, S0354:1, H0580:1, H0741:1, H0586:1, H0559:1, H0486:1, L0021:1, H0618:1, H0009:1, H0571:1, S0051:1, S0368:1, H0553:1, H0181:1, H0551:1, S0294:1, L3905:1, L0646:1, L0764:1, L0662:1, L0794:1, L0658:1, L0659:1, L0665:1, H0547:1, H0682:1, H0684:1, H0670:1 and S3014:1.
30	HDPBA28	1062783	40	AR249:72, AR213:48, AR253:40, AR096:37, AR052:37, AR263:33, AR053:32, AR212:31, AR265:27, AR184:26, AR254:26, AR264:22, AR248:18, AR251:17, AR240:17, AR313:16, AR268:14, AR272:13, AR290:13, AR311:13, AR310:13, AR177:13, AR180:13, AR246:13, AR245:10, AR250:10, AR309:10, AR275:10, AR183:9, AR247:9, AR274:9, AR312:9, AR039:9, AR308:9, AR269:9, AR271:8, AR179:8, AR270:8, AR267:8, AR316:7, AR198:7, AR252:7, AR244:7, AR243:7, AR175:6, AR193:6, AR195:6, AR165:6, AR299:6, AR192:6, AR166:6, AR201:6, AR164:6, AR162:6, AR161:6, AR242:6, AR163:6, AR273:6, AR300:5, AR197:5, AR284:5, AR282:5, AR055:5, AR181:4, AR169:4, AR174:4, AR185:4, AR061:4, AR089:4, AR298:4, AR259:4, AR234:4, AR293:3, AR182:3, AR202:3, AR205:3, AR231:3, AR215:3, AR283:3, AR236:3, AR225:3, AR173:2, AR178:2, AR060:2, AR294:2, AR186:2, AR296:2, AR222:2, AR285:2, AR281:2, AR104:2, AR292:2, AR176:2, AR295:2, AR207:2, AR217:2, AR229:2, AR289:2, AR226:2, AR291:2, AR206:2, AR172:2, AR288:2, AR033:2, AR235:2, AR238:2, AR191:2, AR170:2, AR194:2, AR232:2, AR230:2, AR286:2, AR189:1, AR257:1, AR190:1, AR199:1, AR277:1, AR287:1, AR200:1, AR224:1, AR171:1, AR297:1, AR223:1, AR168:1, AR228:1, AR266:1, AR258:1, AR233:1, AR204:1, AR262:1, AR315:1, AR255:1, AR237:1, AR280:1 H0521:4, L0454:2, S0442:2, L0758:2, H0720:1, H0255:1, S0376:1, H0486:1, H0581:1, H0373:1, H0268:1, S0440:1, L0763:1, L0803:1, H0435:1, H0658:1, L3833:1, H0522:1, L0748:1, L0749:1, L0588:1 and H0543:1.
	HDPBA28	866429	204	
31	HDPCL63	1019008	41	AR281:19, AR202:15, AR194:15, AR196:14, AR315:13, AR207:13, AR206:13, AR265:13, AR205:12, AR244:12, AR195:12, AR222:11, AR033:11, AR235:10, AR214:10, AR263:10, AR225:10, AR218:10, AR246:10, AR197:10, AR261:10, AR284:10, AR310:10, AR170:10, AR242:10, AR224:10, AR198:10, AR162:10, AR311:9, AR161:9, AR172:9, AR192:9, AR241:9, AR169:9, AR223:9, AR171:9, AR291:9, AR183:9, AR314:9, AR273:9, AR215:9, AR163:9, AR298:9, AR216:8, AR295:8, AR217:8, AR174:8, AR240:8, AR280:8, AR282:8, AR275:8, AR193:8, AR181:8, AR243:8, AR245:8, AR252:8, AR221:8, AR168:8, AR264:8, AR219:8, AR285:8, AR271:8, AR165:7, AR176:7, AR177:7, AR201:7, AR296:7, AR211:7, AR191:7, AR270:7, AR212:7, AR175:7, AR164:7, AR269:7, AR247:7, AR184:7, AR289:7, AR288:7, AR309:7, AR286:7, AR210:7, AR213:7, AR268:7, AR250:7, AR200:7, AR287:7, AR189:7, AR292:7, AR053:7, AR266:7, AR104:6, AR173:6, AR204:6, AR297:6, AR283:6, AR272:6, AR290:6, AR236:6, AR182:6, AR312:6, AR308:6, AR180:6, AR096:6, AR277:6, AR188:6, AR293:6, AR186:6, AR299:6, AR190:5, AR052:5, AR300:5, AR199:5, AR039:5, AR251:5, AR089:5, AR249:5, AR178:5,

				AR231:5, AR294:5, AR248:5, AR274:5, AR316:5, AR055:4, AR232:4, AR257:4, AR267:4, AR313:4, AR262:4, AR258:4, AR234:4, AR238:4, AR229:4, AR203:4, AR254:4, AR256:3, AR061:3, AR255:3, AR179:3, AR226:3, AR185:3, AR259:3, AR227:3, AR260:3, AR230:3, AR060:3, AR239:3, AR233:3, AR237:3, AR253:2, AR228:2 L0751:8, L0439:6, L0659:5, L0438:4, L0744:4, L0754:4, L0777:4, S0046:3, H0052:3, H0009:3, H0271:3, L0662:3, L0665:3, L0747:3, H0740:2, S0358:2, H0586:2, H0251:2, H0100:2, L3905:2, L0794:2, L0803:2, L0809:2, H0519:2, S0126:2, L0749:2, L0731:2, L0757:2, L0605:2, H0170:1, H0717:1, H0295:1, H0294:1, L0785:1, S0116:1, H0483:1, L3659:1, S0418:1, H0742:1, H0735:1, S0045:1, H0619:1, H0550:1, H0370:1, H0592:1, H0574:1, H0427:1, H0599:1, T0082:1, S0010:1, S0049:1, H0544:1, H0545:1, H0570:1, H0051:1, S0388:1, H0356:1, H0399:1, H0266:1, H0622:1, L0194:1, H0135:1, H0412:1, H0623:1, H0059:1, L0351:1, T0042:1, H0561:1, S0294:1, L0640:1, L4747:1, L5575:1, L5565:1, L0800:1, L0764:1, L0648:1, L0768:1, L0774:1, L0776:1, L0657:1, L0559:1, L0519:1, L0789:1, L0792:1, L0666:1, L0664:1, L0709:1, L3811:1, H0520:1, H0547:1, S0328:1, S0378:1, H0754:1, S0152:1, H0521:1, S0190:1, S0406:1, H0436:1, L0748:1, L0780:1, L0759:1, L0601:1, L0366:1 and H0423:1.
	HDPCL63	847045	205	
	HDPCL63	897484	206	
32	HDPCO25	460682	42	AR060:2, AR055:2, AR282:2 H0521:2, H0445:2, H0394:1, H0747:1, H0581:1, L0761:1 and L0750:1.
33	HDPFP29	628254	43	AR311:15, AR263:15, AR223:14, AR224:14, AR264:14, AR214:14, AR195:13, AR215:12, AR222:12, AR168:12, AR309:12, AR225:12, AR169:12, AR161:11, AR162:11, AR235:11, AR163:11, AR171:11, AR253:11, AR217:11, AR089:10, AR213:10, AR212:10, AR252:10, AR207:10, AR165:10, AR240:10, AR172:10, AR216:10, AR192:9, AR053:9, AR221:9, AR166:9, AR164:9, AR170:9, AR245:9, AR308:9, AR196:8, AR282:8, AR312:8, AR039:8, AR246:8, AR254:8, AR295:8, AR198:8, AR288:8, AR096:7, AR316:7, AR193:7, AR277:7, AR181:7, AR177:7, AR261:7, AR250:7, AR299:7, AR060:7, AR189:7, AR205:7, AR174:6, AR274:6, AR191:6, AR229:6, AR271:6, AR201:6, AR243:6, AR188:6, AR210:6, AR268:6, AR247:6, AR285:6, AR269:6, AR197:6, AR173:6, AR313:6, AR199:6, AR272:6, AR183:5, AR175:5, AR289:5, AR300:5, AR297:5, AR275:5, AR200:5, AR185:5, AR218:5, AR180:5, AR190:5, AR178:5, AR238:5, AR055:5, AR262:5, AR211:5, AR291:5, AR290:5, AR033:5, AR270:5, AR203:5, AR176:5, AR296:5, AR104:5, AR293:5, AR219:5, AR287:5, AR286:5, AR255:5, AR236:5, AR204:5, AR234:4, AR294:4, AR257:4, AR266:4, AR179:4, AR283:4, AR239:4, AR231:4, AR242:4, AR182:4, AR232:4, AR258:4, AR061:3, AR226:3, AR230:3, AR267:3, AR233:3, AR227:3, AR237:3, AR256:3, AR228:3, AR260:2 S0474:6, L0766:6, L0662:4, L0748:4, H0556:3, L0387:3, L0659:3, L0779:3, H0255:2, H0402:2, S0360:2, S0408:2, S0410:2, H0309:2, H0591:2, H0087:2, L0764:2, L0809:2, L0666:2, L0663:2, H0648:2, L0751:2, L0754:2, L0747:2, H0295:1, S0116:1, H0306:1, S0376:1, H0747:1, H0749:1, H0771:1, H0455:1, L0623:1, H0581:1, H0052:1, H0569:1, H0123:1, H0428:1, H0039:1, H0622:1, T0006:1, H0628:1, H0673:1, L0369:1, L0770:1, L0769:1, L0638:1, L0761:1, L0667:1, L0772:1, L0643:1, L0771:1, L0794:1, L0803:1, L0804:1, L0774:1, L0806:1, L0805:1, L0655:1, L0657:1, L0658:1, L0783:1, L0519:1, L0789:1, L0352:1, S0378:1, H0521:1, H0478:1, L0744:1, L0439:1, L0777:1, L0753:1 and S0434:1.
34	HDPGT01	771583	44	AR268:5, AR244:4, AR282:3, AR251:3, AR242:3, AR241:3, AR052:3, AR184:2, AR271:2, AR310:2, AR176:2, AR194:2, AR039:2, AR309:2, AR283:1, AR178:1, AR289:1, AR217:1, AR257:1, AR277:1, AR170:1, AR284:1, AR221:1, AR226:1, AR265:1 H0521:3, S0278:2, S0222:2, H0284:2, H0265:1, H0728:1, S0007:1, H0208:1, H0586:1, H0497:1, H0642:1, H0581:1, H0052:1, H0572:1, H0024:1, H0292:1, H0428:1, H0628:1, H0135:1, H0163:1, H0433:1, S0002:1, L2263:1, L0438:1, L3829:1, H0539:1, S0027:1, S0032:1, L0439:1, S0436:1, S0458:1 and H0352:1.

35	HDPHI51	460679	45	AR195:9, AR192:9, AR207:9, AR215:8, AR264:8, AR225:7, AR263:7, AR311:7, AR168:7, AR309:7, AR252:6, AR172:6, AR245:6, AR161:6, AR162:6, AR163:6, AR196:6, AR223:6, AR193:6, AR177:6, AR246:6, AR224:6, AR197:5, AR308:5, AR272:5, AR214:5, AR275:5, AR222:5, AR253:5, AR176:5, AR261:5, AR295:5, AR291:5, AR171:5, AR218:5, AR221:5, AR219:5, AR188:5, AR165:5, AR096:5, AR217:5, AR238:5, AR288:5, AR164:5, AR175:5, AR166:5, AR089:5, AR271:5, AR060:4, AR240:4, AR183:4, AR201:4, AR257:4, AR169:4, AR312:4, AR316:4, AR039:4, AR274:4, AR190:4, AR191:4, AR181:4, AR178:4, AR236:4, AR216:4, AR180:4, AR205:4, AR210:4, AR270:4, AR170:4, AR277:4, AR243:4, AR235:4, AR212:4, AR104:4, AR199:4, AR189:4, AR242:4, AR213:4, AR255:4, AR289:4, AR174:3, AR285:3, AR230:3, AR286:3, AR297:3, AR299:3, AR283:3, AR313:3, AR204:3, AR287:3, AR173:3, AR247:3, AR229:3, AR269:3, AR296:3, AR182:3, AR293:3, AR266:3, AR258:3, AR198:3, AR237:3, AR262:3, AR033:3, AR239:3, AR185:3, AR231:3, AR203:3, AR200:3, AR179:3, AR211:3, AR227:3, AR268:3, AR267:3, AR294:3, AR290:3, AR234:3, AR232:3, AR226:3, AR300:2, AR250:2, AR282:2, AR256:2, AR061:2, AR053:2, AR233:2, AR260:2, AR228:2, AR055:2 H0521:1
36	HDPJM30	879325	46	AR268:8, AR289:6, AR184:6, AR266:5, AR252:5, AR223:5, AR169:5, AR290:4, AR286:4, AR224:4, AR194:4, AR257:4, AR214:4, AR310:4, AR270:4, AR165:4, AR294:3, AR291:3, AR222:3, AR183:3, AR235:3, AR215:3, AR282:3, AR284:3, AR297:3, AR267:3, AR260:3, AR217:2, AR262:2, AR182:2, AR258:2, AR309:2, AR172:2, AR288:2, AR298:2, AR225:2, AR269:2, AR296:2, AR176:2, AR248:2, AR166:2, AR216:2, AR250:2, AR292:2, AR164:2, AR263:2, AR162:2, AR287:2, AR255:2, AR053:2, AR061:2, AR249:2, AR163:2, AR293:2, AR285:2, AR253:2, AR312:2, AR178:2, AR313:2, AR277:2, AR256:2, AR205:2, AR052:1, AR203:1, AR238:1, AR274:1, AR171:1, AR295:1, AR231:1, AR247:1, AR206:1, AR181:1, AR221:1, AR226:1, AR230:1, AR179:1, AR283:1, AR232:1, AR200:1, AR239:1, AR186:1, AR237:1, AR195:1, AR228:1, AR240:1, AR233:1, AR227:1, AR246:1, AR199:1, AR173:1, AR243:1, AR089:1, AR177:1 L0800:4, H0617:3, H0521:3, L0070:3, L0742:3, L0770:2, L0771:2, L0794:2, H0689:2, L0741:2, L0439:2, H0445:2, H0224:1, H0637:1, H0370:1, H0250:1, H0052:1, H0194:1, L0455:1, S0422:1, L0761:1, L0764:1, L0806:1, L0659:1, L5622:1, L0789:1, L0790:1, L0792:1, H0672:1, S0152:1, S0434:1 and S0436:1.
	HDPJM30	603517	207	
37	HDPMM88	972734	47	AR202:35, AR096:34, AR194:33, AR206:31, AR244:25, AR241:22, AR268:21, AR281:20, AR290:19, AR265:17, AR315:15, AR184:15, AR246:15, AR310:14, AR192:13, AR269:12, AR270:12, AR282:12, AR243:11, AR314:11, AR280:11, AR267:10, AR292:10, AR183:9, AR263:9, AR299:9, AR284:9, AR198:9, AR055:8, AR205:8, AR251:8, AR273:8, AR266:8, AR313:8, AR298:8, AR283:8, AR039:8, AR033:8, AR204:7, AR052:7, AR277:7, AR177:7, AR238:7, AR234:7, AR061:6, AR247:6, AR295:6, AR104:6, AR300:6, AR285:6, AR089:6, AR316:6, AR186:6, AR185:6, AR240:5, AR053:5, AR249:5, AR231:5, AR271:5, AR291:5, AR289:5, AR182:5, AR312:5, AR175:4, AR253:4, AR229:4, AR248:4, AR232:4, AR309:4, AR215:4, AR226:4, AR274:4, AR219:4, AR286:4, AR296:4, AR227:4, AR237:4, AR218:4, AR259:3, AR275:3, AR294:3, AR213:3, AR242:3, AR179:3, AR293:3, AR060:3, AR170:3, AR193:3, AR233:3, AR169:2, AR224:2, AR256:2, AR257:2, AR258:2, AR171:2, AR217:2, AR172:2, AR264:1, AR195:1, AR308:1, AR163:1, AR261:1, AR161:1, AR162:1, AR199:1, AR221:1 L0754:2, L0777:2, H0717:1, H0740:1, S0212:1, S0360:1, S0408:1, H0747:1, H0004:1, H0581:1, L0142:1, H0674:1, H0646:1, S0422:1, L0809:1, L0787:1, H0521:1 and H0522:1.
	HDPMM88	906121	208	
	HDPMM88	902299	209	

	HDPMM88	885059	210	
	HDPMM88	874074	211	
	HDPMM88	854246	212	
	HDPMM88	854245	213	
38	HDPOJ08	731863	48	AR250:19, AR254:19, AR269:19, AR268:16, AR248:16, AR290:15, AR249:13, AR270:12, AR253:12, AR183:10, AR267:10, AR180:10, AR161:9, AR162:9, AR165:9, AR164:9, AR163:9, AR181:8, AR166:8, AR173:8, AR174:8, AR184:7, AR235:7, AR252:7, AR229:7, AR272:7, AR176:7, AR177:6, AR178:6, AR265:6, AR239:6, AR182:6, AR175:6, AR096:6, AR291:5, AR189:5, AR288:5, AR287:5, AR190:5, AR251:5, AR263:5, AR230:5, AR179:5, AR228:5, AR236:4, AR234:4, AR257:4, AR193:4, AR238:4, AR237:4, AR285:4, AR233:4, AR289:4, AR185:4, AR311:4, AR286:4, AR308:4, AR226:4, AR282:4, AR264:4, AR240:4, AR232:4, AR201:4, AR261:4, AR292:4, AR089:4, AR210:4, AR212:4, AR295:4, AR247:4, AR297:4, AR275:4, AR262:4, AR245:4, AR195:4, AR188:4, AR231:4, AR197:4, AR309:4, AR196:4, AR284:4, AR191:4, AR299:4, AR313:3, AR255:3, AR199:3, AR200:3, AR293:3, AR300:3, AR316:3, AR296:3, AR246:3, AR203:3, AR243:3, AR294:3, AR214:3, AR274:3, AR104:3, AR060:3, AR219:3, AR298:3, AR033:3, AR227:3, AR053:3, AR221:2, AR271:2, AR312:2, AR223:2, AR218:2, AR061:2, AR259:2, AR224:2, AR217:2, AR277:2, AR225:2, AR258:2, AR215:2, AR039:2, AR168:2, AR266:2, AR211:2, AR055:2, AR222:2, AR205:2, AR216:2, AR202:1, AR213:1, AR260:1, AR256:1, AR314:1 S0474:29, L0766:11, H0521:10, L0803:7, L0748:6, L0717:5, L0759:5, S0003:4, L3832:4, H0663:3, H0156:3, L0598:3, L0770:3, L0771:3, L0804:3, L2439:3, H0522:3, L0731:3, S0436:3, H0486:2, S0426:2, L0805:2, L0659:2, L2260:2, S0126:2, S0406:2, L0749:2, L0755:2, L0757:2, L0758:2, L0590:2, S0026:2, H0716:1, H0341:1, S0212:1, L0481:1, S0444:1, S0360:1, L3649:1, H0637:1, H0580:1, H0734:1, H0749:1, L3092:1, H0619:1, L3388:1, H0586:1, H0574:1, H0427:1, L0021:1, H0575:1, H0318:1, H0545:1, H0024:1, H0373:1, H0071:1, H0179:1, S0214:1, H0428:1, H0674:1, H0591:1, H0616:1, H0488:1, H0494:1, S0438:1, S0440:1, H0647:1, S0142:1, UNKWN:1, L0369:1, L0763:1, L0769:1, L0646:1, L0648:1, L0662:1, L0650:1, L0775:1, L0653:1, L0776:1, L0656:1, L0782:1, L0809:1, L0519:1, S0052:1, L2657:1, H0144:1, L3823:1, H0520:1, H0547:1, H0660:1, S0380:1, L0742:1, L0439:1, L0750:1, L0777:1, S0031:1, H0445:1, S0434:1, H0665:1, H0667:1, S0194:1, S0276:1 and S0458:1.
39	HDPPN86	1037893	49	AR212:4, AR235:3, AR266:2, AR221:2, AR207:2, AR205:2, AR216:2, AR168:2, AR282:2, AR257:2, AR181:1, AR311:1, AR271:1, AR161:1, AR264:1, AR165:1, AR172:1, AR295:1, AR164:1, AR162:1, AR176:1, AR163:1, AR171:1, AR285:1, AR289:1, AR277:1, AR238:1, AR089:1, AR234:1, AR211:1 H0542:4, S0418:3, H0543:3, S0038:2, H0341:1, L0018:1, H0069:1, H0090:1, H0056:1, H0494:1, H0522:1 and H0423:1.
	HDPPN86	895711	214	
40	HDPSB18	1043263	50	AR197:9, AR060:8, AR253:8, AR161:8, AR162:8, AR163:8, AR165:8, AR164:7, AR089:7, AR166:7, AR204:7, AR192:7, AR207:7, AR177:6, AR193:6, AR185:6, AR235:6, AR271:6, AR195:6, AR053:6, AR312:6, AR233:6, AR232:6, AR174:5, AR282:5, AR104:5, AR299:5, AR227:5, AR212:5, AR181:5, AR309:5, AR264:5, AR205:5, AR308:5, AR178:5, AR237:5, AR061:5, AR313:5, AR300:5, AR175:5, AR263:5, AR247:5, AR223:5, AR173:5, AR226:5, AR272:5, AR243:5, AR240:5, AR311:5, AR055:5, AR269:5, AR201:4, AR229:4, AR286:4, AR182:4, AR246:4, AR236:4, AR295:4, AR316:4, AR285:4, AR261:4, AR293:4, AR275:4, AR291:4, AR228:4, AR274:4, AR296:4, AR176:4, AR213:4, AR297:4, AR179:4, AR270:4,

				AR254:4, AR039:4, AR239:4, AR262:4, AR288:4, AR180:4, AR287:4, AR096:4, AR238:4, AR183:4, AR203:4, AR033:4, AR257:4, AR234:4, AR230:4, AR294:3, AR198:3, AR289:3, AR255:3, AR266:3, AR258:3, AR267:3, AR283:3, AR168:3, AR217:3, AR231:3, AR214:3, AR277:3, AR252:3, AR196:3, AR250:3, AR218:3, AR245:3, AR190:2, AR216:2, AR268:2, AR224:2, AR290:2, AR188:2, AR191:2, AR189:2, AR221:2, AR260:2, AR222:2, AR200:2, AR171:2, AR211:2, AR210:2, AR219:2, AR172:2, AR199:2, AR215:1, AR170:1, AR225:1, AR256:1 L0769:5, L0774:3, H0656:2, S0442:2, S0358:2, S0360:2, S0278:2, H0620:2, L0500:2, L0775:2, L0710:2, L0777:2, L0752:2, L0588:2, H0149:1, H0295:1, T0049:1, H0381:1, H0484:1, H0483:1, H0638:1, S0420:1, S0444:1, S0408:1, S0045:1, H0587:1, H0318:1, H0204:1, H0530:1, H0545:1, H0178:1, L0471:1, L0142:1, H0181:1, H0087:1, H0412:1, H0623:1, H0100:1, S0438:1, H0633:1, H0646:1, H0529:1, L0506:1, L0761:1, L0764:1, L0648:1, L0766:1, L0497:1, L0493:1, L0511:1, L0665:1, L2260:1, H0698:1, H0690:1, H0521:1, S0406:1, S3014:1, L0747:1, L0780:1, H0543:1 and H0422:1.
	HDPSB18	903816	215	
	HDPSB18	905414	216	
	HDPSB18	732097	217	
41	HDPSH53	1309174	51	AR214:47, AR207:47, AR263:40, AR222:34, AR169:33, AR235:33, AR212:31, AR213:30, AR223:29, AR170:29, AR311:29, AR309:28, AR168:28, AR195:27, AR264:26, AR192:26, AR224:26, AR216:24, AR295:24, AR171:24, AR245:24, AR217:23, AR172:23, AR198:22, AR308:22, AR271:22, AR161:21, AR162:21, AR163:21, AR252:21, AR261:21, AR288:21, AR053:20, AR166:20, AR197:20, AR242:20, AR201:20, AR033:19, AR205:19, AR177:19, AR312:19, AR193:19, AR165:18, AR240:18, AR229:18, AR277:18, AR254:18, AR164:18, AR225:17, AR246:17, AR297:17, AR236:17, AR285:16, AR291:16, AR275:16, AR238:16, AR272:16, AR174:15, AR296:15, AR274:15, AR232:15, AR286:14, AR282:14, AR230:13, AR181:13, AR211:13, AR250:13, AR226:13, AR239:13, AR287:12, AR227:12, AR283:12, AR247:12, AR237:12, AR289:12, AR215:12, AR316:12, AR204:12, AR210:12, AR176:12, AR180:12, AR293:12, AR231:11, AR270:11, AR300:11, AR299:11, AR262:11, AR175:11, AR185:11, AR243:11, AR196:11, AR221:11, AR258:10, AR269:10, AR200:10, AR313:10, AR089:10, AR253:10, AR183:10, AR294:10, AR268:9, AR061:9, AR104:9, AR173:9, AR234:9, AR199:9, AR096:9, AR179:9, AR218:8, AR178:8, AR233:8, AR257:8, AR219:8, AR255:8, AR266:8, AR290:8, AR267:8, AR188:8, AR228:8, AR189:7, AR055:7, AR060:7, AR203:7, AR191:7, AR256:7, AR039:7, AR260:6, AR182:6, AR190:6 L0804:2, H0521:2, L0021:1, H0617:1, H0623:1, L0648:1 and L0665:1.
	HDPSH53	1040056	218	
	HDPSH53	882768	219	
42	HDPSP01	1352280	52	AR169:8, AR235:5, AR265:5, AR180:4, AR176:4, AR161:4, AR163:4, AR311:4, AR162:4, AR269:3, AR165:3, AR172:3, AR171:3, AR222:3, AR166:3, AR183:3, AR225:3, AR168:3, AR282:3, AR224:3, AR245:3, AR272:3, AR196:3, AR223:3, AR297:3, AR221:2, AR182:2, AR298:2, AR164:2, AR261:2, AR257:2, AR170:2, AR270:2, AR289:2, AR216:2, AR173:2, AR191:2, AR214:2, AR287:2, AR296:2, AR242:2, AR228:2, AR247:2, AR295:2, AR255:2, AR192:2, AR240:2, AR174:2, AR227:2, AR053:2, AR275:2, AR203:2, AR266:2, AR288:2, AR215:2, AR277:2, AR239:2, AR291:2, AR264:2, AR263:2, AR285:2, AR230:2, AR190:2, AR310:2, AR189:2, AR274:1, AR181:1, AR286:1, AR179:1, AR226:1, AR246:1, AR231:1, AR178:1, AR175:1, AR238:1, AR233:1, AR273:1, AR290:1, AR243:1, AR200:1, AR293:1, AR294:1, AR309:1, AR284:1,

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	HDPSP01	689129	220	
43	HDPSP54	744440	53	AR263:53, AR207:53, AR214:51, AR169:41, AR224:40, AR222:38, AR223:37, AR195:36, AR235:32, AR217:31, AR212:31, AR168:30, AR172:30, AR311:29, AR053:28, AR192:28, AR196:28, AR171:27, AR198:27, AR213:27, AR221:27, AR161:26, AR264:26, AR252:26, AR162:25, AR170:25, AR210:25, AR245:24, AR033:23, AR225:23, AR216:23, AR163:22, AR089:22, AR261:22, AR215:21, AR271:21, AR177:21, AR181:21, AR104:21, AR295:20, AR218:20, AR236:19, AR193:19, AR191:19, AR211:19, AR197:18, AR185:18, AR055:18, AR219:18, AR201:18, AR240:18, AR165:17, AR316:17, AR166:17, AR299:17, AR164:17, AR060:17, AR253:17, AR174:16, AR242:16, AR288:16, AR199:16, AR205:16, AR246:15, AR282:15, AR039:15, AR238:15, AR308:15, AR229:15, AR175:14, AR188:14, AR285:14, AR297:14, AR254:14, AR189:14, AR232:14, AR277:13, AR300:13, AR287:13, AR243:13, AR230:13, AR312:13, AR291:13, AR286:12, AR204:12, AR250:12, AR226:12, AR173:12, AR200:12, AR239:12, AR176:12, AR274:11, AR296:11, AR096:11, AR309:11, AR203:11, AR231:11, AR270:11, AR247:11, AR293:11, AR190:11, AR283:10, AR258:10, AR267:10, AR234:10, AR289:10, AR262:10, AR178:10, AR268:10, AR227:10, AR313:10, AR180:10, AR237:10, AR179:9, AR257:9, AR182:9, AR269:9, AR255:9, AR233:9, AR260:9, AR061:9, AR183:9, AR290:8, AR275:8, AR272:8, AR266:8, AR294:7, AR256:7, AR228:6 L0740:8, L0662:3, L0659:3, L0663:3, S0422:2, L0646:2, L0766:2, L0439:2, L0779:2, H0171:1, S6024:1, S0110:1, S0360:1, H0411:1, H0455:1, S0474:1, H0510:1, S0438:1, L0637:1, L5565:1, L0771:1, L0773:1, L0794:1, L0804:1, L0787:1, L0665:1, L0438:1, H0521:1, S0406:1, L0754:1, L0755:1 and L0758:1.
	HDPSP54	502472	221	
44	HDPUW68	812737	54	AR253:15, AR052:14, AR213:11, AR184:11, AR230:11, AR228:9, AR170:9, AR250:8, AR168:8, AR254:8, AR225:6, AR297:6, AR053:6, AR251:5, AR267:5, AR248:5, AR268:5, AR221:5, AR096:5, AR214:5, AR238:5, AR178:5, AR249:5, AR216:5, AR173:5, AR239:5, AR236:5, AR166:5, AR182:4, AR161:4, AR162:4, AR217:4, AR269:4, AR282:4, AR163:4, AR224:4, AR222:4, AR237:4, AR296:4, AR257:4, AR263:4, AR244:4, AR227:4, AR258:4, AR252:4, AR291:4, AR229:4, AR219:4, AR287:4, AR290:4, AR275:4, AR264:4, AR183:4, AR175:4, AR223:4, AR199:4, AR308:4, AR171:3, AR194:3, AR246:3, AR277:3, AR260:3, AR288:3, AR240:3, AR274:3, AR191:3, AR284:3, AR243:3, AR312:3, AR293:3, AR179:3, AR233:3, AR300:3, AR261:3, AR218:3, AR165:3, AR061:3, AR231:3, AR033:3, AR298:3, AR316:3, AR164:3, AR181:3, AR255:3, AR270:3, AR189:3, AR313:3, AR309:3, AR234:2, AR186:2, AR247:2, AR195:2, AR285:2, AR232:2, AR292:2, AR185:2, AR226:2, AR180:2, AR299:2, AR289:2, AR271:2, AR193:2, AR089:2, AR203:2, AR311:2, AR060:2, AR172:2, AR310:2, AR215:2, AR177:2, AR266:2, AR262:2, AR272:2, AR188:2, AR196:2, AR169:1, AR212:1, AR210:1, AR055:1, AR283:1, AR190:1, AR241:1, AR295:1, AR286:1, AR201:1, AR294:1, AR104:1, AR256:1, AR205:1, AR039:1 H0677:47, H0521:14, H0295:3, H0587:3, H0556:2, H0656:2, H0638:2, H0411:2, S0002:2, L0766:2, L0776:2, L0659:2, L0809:2, H0670:2, H0522:2, S0404:2, L0743:2, L0744:2, L0740:2, L0731:2, S0134:1, H0657:1, H0254:1, S0476:1, S0278:1, H0486:1, H0575:1, H0606:1, H0135:1, H0561:1, S0438:1, L0761:1, L0768:1, L0655:1, L2261:1, S0374:1, H0690:1, H0435:1, H0658:1,

				H0696:1, H0678:1, L0779:1, L0752:1, H0445:1, S0434:1 and S0436:1.
45	HDPXY01	879048	55	AR207:8, AR165:8, AR245:8, AR214:8, AR164:8, AR275:8, AR163:8, AR162:8, AR263:8, AR169:8, AR195:7, AR166:7, AR274:7, AR161:7, AR309:7, AR272:7, AR170:7, AR212:7, AR308:6, AR311:6, AR198:6, AR089:6, AR060:6, AR197:6, AR192:6, AR264:6, AR039:6, AR177:6, AR243:6, AR223:6, AR235:5, AR213:5, AR096:5, AR282:5, AR168:5, AR313:5, AR222:5, AR240:5, AR204:5, AR217:5, AR261:5, AR193:4, AR312:4, AR104:4, AR224:4, AR246:4, AR176:4, AR055:4, AR299:4, AR171:4, AR283:4, AR271:4, AR277:4, AR174:4, AR316:4, AR178:4, AR295:4, AR053:4, AR205:4, AR185:4, AR237:4, AR033:4, AR247:4, AR300:4, AR266:4, AR257:3, AR270:3, AR181:3, AR293:3, AR233:3, AR250:3, AR225:3, AR288:3, AR291:3, AR216:3, AR296:3, AR201:3, AR286:3, AR285:3, AR268:3, AR228:3, AR297:3, AR254:3, AR294:3, AR252:3, AR269:3, AR229:3, AR287:3, AR232:3, AR061:3, AR234:3, AR289:3, AR183:3, AR227:3, AR231:3, AR211:3, AR267:3, AR230:3, AR255:3, AR236:3, AR239:2, AR226:2, AR179:2, AR200:2, AR182:2, AR262:2, AR175:2, AR203:2, AR180:2, AR290:2, AR196:2, AR199:2, AR189:2, AR258:2, AR173:2, AR210:2, AR191:2, AR238:1, AR190:1, AR253:1, AR215:1, AR172:1 L0646:4, L0666:4, L0662:3, L0749:3, H0661:2, H0620:2, H0617:2, H0144:2, L0777:2, L0731:2, H0170:1, S0360:1, S0046:1, L0717:1, H0013:1, H0052:1, H0039:1, H0622:1, H0606:1, H0673:1, L0769:1, L0796:1, L5565:1, L5566:1, L0764:1, L0648:1, L0381:1, L0805:1, L0659:1, L0789:1, L0792:1, L0663:1, L0665:1, H0689:1, H0660:1, H0648:1, H0539:1, H0521:1, L0779:1 and L0603:1.
	HDPXY01	904768	222	
	HDPXY01	895716	223	
	HDPXY01	895715	224	
46	HDTBD53	972757	56	AR242:4, AR246:4, AR250:3, AR263:3, AR195:3, AR272:3, AR264:3, AR170:3, AR282:3, AR215:3, AR163:3, AR162:3, AR235:3, AR089:3, AR198:3, AR165:3, AR161:3, AR197:2, AR266:2, AR053:2, AR169:2, AR212:2, AR205:2, AR285:2, AR243:2, AR312:2, AR240:2, AR270:2, AR221:2, AR296:2, AR213:2, AR178:2, AR216:2, AR261:2, AR214:2, AR299:2, AR247:2, AR060:2, AR164:2, AR267:1, AR237:1, AR183:1, AR271:1, AR172:1, AR286:1, AR179:1, AR166:1, AR291:1, AR311:1, AR316:1, AR313:1, AR288:1, AR171:1, AR188:1, AR268:1, AR269:1, AR308:1, AR173:1, AR287:1, AR297:1, AR033:1 L0439:17, L0731:17, L0747:16, L0766:13, S0360:8, L0770:8, L0659:8, L0754:8, H0553:7, L0663:7, L0749:7, L0758:7, H0486:6, S0192:6, L0662:5, L0105:4, H0644:4, L0438:4, H0547:4, L0748:4, L0751:4, L0752:4, L0755:4, L0599:4, H0542:4, H0556:3, H0662:3, S0420:3, H0599:3, H0050:3, H0266:3, H0622:3, H0135:3, H0551:3, H0529:3, L0783:3, H0519:3, H0670:3, H0521:3, H0555:3, L0750:3, H0717:2, H0663:2, H0638:2, S0476:2, H0592:2, H0013:2, H0598:2, H0090:2, H0038:2, H0040:2, H0494:2, S0440:2, S0344:2, L0638:2, L0761:2, L0764:2, L0649:2, L0774:2, L0775:2, L0657:2, L0787:2, L0666:2, H0144:2, L0565:2, H0659:2, S0044:2, L0759:2, S0194:2, H0422:2, H0170:1, S0040:1, H0713:1, T0049:1, S0134:1, S0110:1, H0402:1, S0356:1, S0442:1, S0354:1, S0376:1, S0444:1, S0410:1, S0300:1, H0369:1, H0261:1, H0549:1, H0550:1, S0222:1, H0586:1, H0587:1, L0586:1, T0060:1, H0244:1, S0280:1, L0021:1, H0025:1, H0421:1, H0309:1, L0040:1, H0544:1, L0471:1, H0024:1, L0163:1, S0388:1, H0188:1, H0687:1, S0003:1, H0615:1, H0039:1, H0030:1, H0674:1, H0212:1, H0068:1, S0366:1, H0163:1, H0591:1, H0634:1, H0616:1, H0412:1, H0413:1, H0623:1, H0561:1, H0641:1, H0647:1, H0652:1, S0144:1, S0142:1, S0002:1, L0369:1, L0769:1, L5575:1, L5565:1, L3905:1, L5566:1, L0772:1, L0800:1, L0771:1, L0521:1, L0768:1, L0794:1, L0381:1, L0806:1, L0654:1, L0655:1, L0636:1, L0384:1, L0809:1, L0528:1, L0788:1, L0789:1, S0126:1, H0689:1, H0682:1, H0658:1, H0648:1, S0328:1, H0539:1, H0696:1, S0406:1, L0740:1, L0757:1, L0603:1, H0665:1,

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	HDTBD53	906342	225	
47	HDTBV77	785879	57	AR183:7, AR184:5, AR269:4, AR207:4, AR245:4, AR270:4, AR182:4, AR214:4, AR172:4, AR223:4, AR263:3, AR272:3, AR180:3, AR176:3, AR268:3, AR309:3, AR175:3, AR164:3, AR282:3, AR166:3, AR222:3, AR225:3, AR216:3, AR308:3, AR052:3, AR247:3, AR289:3, AR165:3, AR266:2, AR312:2, AR162:2, AR169:2, AR291:2, AR297:2, AR284:2, AR193:2, AR205:2, AR257:2, AR296:2, AR267:2, AR195:2, AR265:2, AR171:2, AR217:2, AR298:2, AR246:2, AR202:2, AR264:2, AR229:2, AR238:2, AR277:2, AR213:2, AR178:2, AR230:2, AR313:2, AR243:2, AR288:2, AR311:2, AR161:2, AR235:2, AR253:2, AR168:2, AR290:2, AR294:2, AR215:2, AR224:2, AR286:2, AR181:2, AR212:2, AR287:2, AR173:2, AR221:2, AR039:2, AR163:2, AR200:2, AR061:2, AR170:2, AR274:2, AR053:2, AR089:2, AR236:2, AR228:2, AR293:2, AR199:2, AR310:1, AR196:1, AR174:1, AR300:1, AR240:1, AR096:1, AR231:1, AR271:1, AR201:1, AR259:1, AR177:1, AR060:1, AR261:1, AR237:1, AR316:1, AR179:1, AR192:1, AR262:1, AR190:1, AR234:1, AR295:1, AR285:1, AR239:1, AR258:1, AR299:1, AR204:1, AR233:1, AR197:1, AR211:1, AR254:1 H0553:3, H0717:2, H0486:1, H0427:1, H0081:1, H0014:1, S0388:1, H0112:1, H0030:1, H0031:1, H0644:1, H0488:1, H0519:1, L0759:1, H0543:1 and H0506:1.
48	HDTDQ23	1306984	58	AR200:16, AR311:15, AR272:13, AR264:12, AR165:11, AR164:11, AR188:11, AR312:10, AR166:10, AR211:10, AR104:10, AR282:10, AR191:10, AR246:9, AR096:9, AR210:9, AR189:9, AR162:9, AR199:9, AR161:9, AR163:9, AR274:9, AR196:9, AR308:8, AR174:8, AR089:8, AR240:8, AR309:7, AR175:7, AR218:7, AR219:7, AR190:7, AR295:7, AR203:7, AR316:7, AR299:7, AR313:6, AR285:6, AR247:6, AR185:6, AR275:6, AR263:6, AR183:6, AR245:6, AR060:6, AR181:6, AR212:6, AR039:6, AR053:5, AR288:5, AR269:5, AR268:5, AR243:5, AR291:5, AR290:5, AR033:5, AR173:5, AR238:5, AR267:5, AR231:5, AR176:5, AR271:5, AR300:4, AR237:4, AR205:4, AR266:4, AR177:4, AR182:4, AR223:4, AR270:4, AR296:4, AR213:4, AR277:4, AR229:4, AR178:4, AR261:4, AR171:4, AR297:3, AR195:3, AR287:3, AR239:3, AR232:3, AR230:3, AR255:3, AR234:3, AR226:3, AR257:3, AR286:3, AR293:3, AR258:3, AR236:3, AR193:3, AR262:3, AR168:3, AR180:3, AR252:3, AR289:3, AR221:3, AR225:3, AR250:3, AR179:3, AR294:3, AR216:2, AR201:2, AR198:2, AR233:2, AR061:2, AR172:2, AR222:2, AR055:2, AR170:2, AR215:2, AR256:2, AR228:2, AR227:2, AR224:2, AR214:1, AR283:1, AR197:1, AR260:1, AR235:1, AR253:1 L0659:5, L0666:4, L0665:4, L2634:3, L0471:2, H0031:2, L0646:2, L0794:2, L0766:2, L0657:2, H0265:1, H0685:1, L0785:1, S0356:1, S0376:1, S0360:1, H0742:1, S0007:1, H0747:1, H0486:1, L2540:1, H0069:1, H0025:1, H0457:1, H0252:1, H0428:1, L0055:1, H0038:1, S0344:1, L0625:1, L0761:1, L0800:1, L0553:1, L0649:1, L0803:1, L0650:1, L0606:1, L3872:1, L0791:1, L0663:1, L0664:1, H0684:1, H0435:1, H0648:1, S0380:1, L3832:1, L0749:1, L0786:1, L0780:1, L0755:1, L0759:1, L0596:1, L0601:1, H0543:1 and H0422:1.
	HDTDQ23	879009	226	
	HDTDQ23	751707	227	
49	HE2DE47	619852	59	AR224:15, AR223:15, AR217:12, AR214:12, AR222:11, AR225:11, AR172:9, AR216:9, AR215:9, AR221:8, AR171:7, AR162:7, AR168:7, AR161:7, AR264:7, AR196:7, AR176:6, AR163:6, AR165:6, AR263:6, AR246:6, AR164:6, AR309:6, AR166:6, AR193:6, AR170:6, AR313:5, AR096:5, AR089:5, AR250:5, AR169:5, AR242:5, AR312:5, AR261:5, AR254:5, AR295:5, AR245:5, AR180:5, AR189:5, AR271:5, AR191:5, AR291:5, AR274:5, AR177:5, AR316:4, AR178:4, AR201:4, AR272:4, AR253:4, AR267:4, AR308:4, AR270:4, AR282:4, AR229:4, AR174:4, AR175:4, AR188:4, AR268:4, AR190:4, AR288:4, AR183:4, AR060:4, AR297:4, AR181:4, AR192:4, AR173:4, AR255:4, AR195:4, AR296:4, AR179:4, AR285:4,

				AR311:4, AR199:4, AR197:4, AR205:4, AR231:4, AR237:4, AR243:4, AR239:4, AR299:4, AR300:3, AR236:3, AR182:3, AR257:3, AR212:3, AR269:3, AR218:3, AR290:3, AR238:3, AR275:3, AR262:3, AR203:3, AR198:3, AR266:3, AR053:3, AR287:3, AR210:3, AR228:3, AR293:3, AR247:3, AR213:3, AR252:3, AR240:3, AR219:3, AR185:3, AR226:3, AR200:3, AR235:3, AR233:3, AR204:3, AR207:3, AR258:3, AR286:3, AR039:3, AR033:2, AR260:2, AR283:2, AR232:2, AR277:2, AR230:2, AR294:2, AR289:2, AR061:2, AR234:2, AR055:2, AR227:2, AR256:2, AR211:2, AR104:2 L0439:10, L0747:9, L0766:8, L0770:5, L0666:4, L0754:4, L0777:4, L0659:3, L0783:3, S0126:3, H0543:3, L0483:2, H0264:2, L0764:2, L0662:2, L0768:2, L0665:2, L0438:2, L0748:2, L0756:2, L0752:2, L0755:2, L0758:2, L0759:2, H0170:1, T0049:1, H0341:1, S0029:1, H0661:1, H0306:1, S0408:1, H0580:1, S0045:1, H0431:1, H0455:1, H0586:1, L0622:1, H0575:1, H0004:1, H0581:1, H0421:1, H0263:1, H0569:1, H0015:1, S0051:1, S0003:1, H0615:1, L0142:1, H0090:1, H0625:1, S0422:1, L0598:1, H0529:1, L0769:1, L0667:1, L0646:1, L0774:1, L0375:1, L0657:1, L0519:1, L0664:1, H0144:1, S0374:1, H0547:1, H0435:1, H0666:1, S0380:1, H0521:1, S0404:1, H0555:1, L0749:1, L0750:1, L0779:1, L0592:1, L0608:1, S0026:1 and H0542:1.
	HE2DE47	382025	228	
50	HE2NV57	740750	60	AR235:6, AR282:4, AR309:4, AR171:4, AR270:4, AR178:3, AR272:3, AR245:3, AR269:3, AR291:3, AR169:3, AR268:3, AR213:3, AR215:3, AR254:3, AR267:3, AR289:3, AR274:3, AR236:3, AR175:3, AR053:3, AR228:3, AR261:3, AR242:2, AR161:2, AR181:2, AR308:2, AR300:2, AR257:2, AR238:2, AR182:2, AR266:2, AR204:2, AR237:2, AR170:2, AR288:2, AR290:2, AR188:2, AR297:2, AR168:2, AR262:2, AR162:2, AR163:2, AR296:2, AR233:2, AR210:2, AR285:2, AR295:2, AR264:2, AR293:2, AR165:2, AR229:2, AR201:2, AR189:2, AR250:2, AR164:2, AR221:2, AR195:2, AR222:2, AR223:2, AR239:2, AR231:2, AR294:2, AR166:2, AR191:2, AR179:2, AR255:2, AR271:2, AR287:2, AR212:2, AR234:2, AR299:2, AR225:2, AR203:2, AR246:2, AR200:2, AR205:1, AR089:1, AR173:1, AR176:1, AR240:1, AR286:1, AR193:1, AR199:1, AR258:1, AR196:1, AR232:1, AR096:1, AR243:1, AR312:1, AR185:1, AR061:1, AR183:1, AR230:1, AR060:1 S0414:3, L0805:3, S0412:3, H0457:2, L0756:2, H0170:1, H0645:1, H0455:1, H0421:1, H0100:1, L0803:1, S0052:1, S0374:1, H0696:1 and L0743:1.
51	HE2PH36	570903	61	AR263:75, AR171:60, AR309:59, AR264:59, AR252:58, AR168:57, AR223:54, AR169:49, AR308:46, AR311:44, AR214:44, AR053:42, AR172:38, AR312:37, AR170:37, AR225:36, AR246:36, AR212:34, AR272:33, AR217:32, AR197:32, AR245:32, AR222:31, AR213:30, AR207:30, AR224:30, AR198:27, AR096:27, AR196:26, AR195:26, AR313:25, AR205:25, AR216:24, AR201:23, AR218:22, AR215:21, AR254:21, AR235:21, AR165:20, AR261:20, AR253:20, AR274:20, AR243:20, AR221:19, AR164:19, AR316:19, AR275:19, AR250:19, AR192:18, AR166:18, AR161:18, AR162:18, AR177:18, AR163:18, AR271:18, AR174:17, AR039:17, AR200:17, AR089:17, AR240:16, AR296:16, AR219:16, AR188:16, AR193:16, AR033:15, AR295:15, AR185:14, AR189:14, AR229:14, AR060:14, AR299:13, AR236:13, AR203:13, AR242:13, AR183:13, AR190:13, AR210:12, AR104:12, AR282:12, AR178:12, AR300:12, AR181:12, AR175:12, AR268:12, AR199:12, AR226:11, AR211:11, AR191:11, AR269:11, AR173:11, AR204:10, AR277:10, AR270:10, AR180:10, AR297:10, AR247:10, AR288:10, AR290:9, AR179:9, AR285:9, AR291:9, AR176:9, AR262:9, AR239:9, AR283:9, AR238:8, AR182:8, AR267:8, AR237:8, AR055:8, AR287:8, AR257:8, AR289:8, AR231:7, AR293:7, AR258:7, AR255:7, AR232:7, AR286:7, AR230:7, AR234:7, AR256:7, AR266:6, AR233:6, AR227:6, AR294:6, AR228:5, AR260:5, AR061:4 H0171:1, S0114:1 and S0356:1.
52	HE8DS15	847060	62	AR180:17, AR181:15, AR178:15, AR096:14, AR182:13, AR179:13, AR246:13, AR175:13, AR191:12, AR183:12, AR190:12, AR240:11, AR268:10, AR270:10, AR174:10, AR269:10, AR173:9, AR243:9, AR176:9, AR060:8, AR185:7, AR255:7,

				AR189:7, AR201:7, AR192:7, AR039:7, AR193:7, AR197:7, AR257:7, AR055:6, AR295:6, AR290:6, AR296:6, AR299:6, AR285:6, AR288:6, AR207:5, AR291:5, AR188:5, AR254:5, AR287:5, AR297:5, AR218:5, AR294:5, AR316:5, AR235:5, AR293:5, AR242:4, AR264:4, AR245:4, AR089:4, AR236:4, AR177:4, AR195:4, AR161:4, AR198:4, AR271:4, AR162:4, AR163:4, AR204:4, AR205:4, AR165:4, AR275:4, AR196:4, AR267:4, AR262:4, AR164:4, AR260:4, AR286:3, AR261:3, AR300:3, AR104:3, AR289:3, AR169:3, AR313:3, AR168:3, AR033:3, AR266:3, AR238:3, AR253:3, AR247:3, AR222:3, AR258:3, AR233:3, AR228:3, AR200:3, AR312:3, AR166:3, AR229:2, AR224:2, AR272:2, AR199:2, AR231:2, AR250:2, AR203:2, AR061:2, AR263:2, AR237:2, AR053:2, AR219:2, AR226:2, AR230:2, AR282:2, AR277:2, AR221:2, AR274:2, AR213:2, AR283:2, AR232:2, AR217:2, AR309:2, AR227:2, AR239:2, AR214:2, AR256:2, AR234:2, AR212:2, AR308:2, AR171:1, AR216:1, AR225:1, AR252:1, AR170:1 L0779:8, L0770:7, L0731:7, L0662:6, L0803:5, L0599:5, L0758:4, H0739:3, H0624:3, H0486:3, H0615:3, L0748:3, L0750:3, H0713:2, S0222:2, H0575:2, H0050:2, H0031:2, H0553:2, S0036:2, H0038:2, S0422:2, L0804:2, L0774:2, L0775:2, L0647:2, L0438:2, L0742:2, L0743:2, L0747:2, L0777:2, L0605:2, L0485:2, H0171:1, H0717:1, S0442:1, H0208:1, H0411:1, H0586:1, H0587:1, L3655:1, H0013:1, H0156:1, H0108:1, H0581:1, S0049:1, H0194:1, H0572:1, H0123:1, L0471:1, H0024:1, H0373:1, S0051:1, S6028:1, H0188:1, H0644:1, H0628:1, H0383:1, H0316:1, T0067:1, L0768:1, L0794:1, L0375:1, L0806:1, L0659:1, L0532:1, L0665:1, H0144:1, H0691:1, S0126:1, H0660:1, H0648:1, S0328:1, S0378:1, S0380:1, H0436:1, S0028:1, L0749:1, L0756:1, L0759:1, H0444:1, S0242:1 and H0352:1.
53	HE9HY07	420063	63	AR172:5, AR201:4, AR266:4, AR170:4, AR269:4, AR182:4, AR168:4, AR039:4, AR176:4, AR228:4, AR169:4, AR236:4, AR254:4, AR165:4, AR257:3, AR164:3, AR233:3, AR253:3, AR191:3, AR166:3, AR183:3, AR181:3, AR229:3, AR264:3, AR268:3, AR178:3, AR231:3, AR237:3, AR270:3, AR180:3, AR283:3, AR179:3, AR053:3, AR197:3, AR190:3, AR096:3, AR060:3, AR239:3, AR055:3, AR177:3, AR238:3, AR255:3, AR193:3, AR312:3, AR061:3, AR250:3, AR235:3, AR267:3, AR230:3, AR185:3, AR288:2, AR175:2, AR293:2, AR196:2, AR262:2, AR246:2, AR316:2, AR287:2, AR033:2, AR294:2, AR089:2, AR247:2, AR313:2, AR173:2, AR243:2, AR300:2, AR234:2, AR271:2, AR290:2, AR199:2, AR297:2, AR277:2, AR286:2, AR224:2, AR223:2, AR309:2, AR289:2, AR200:2, AR174:2, AR296:2, AR232:2, AR163:2, AR226:2, AR211:2, AR285:2, AR222:2, AR299:2, AR261:2, AR189:2, AR205:2, AR162:2, AR203:2, AR295:2, AR240:2, AR227:2, AR171:2, AR260:1, AR214:1, AR216:1, AR311:1, AR212:1, AR188:1, AR219:1, AR291:1, AR221:1, AR272:1, AR308:1, AR161:1, AR245:1 H0615:1 and H0144:1.
54	HEOMQ63	603533	64	AR039:7, AR221:4, AR271:4, AR309:3, AR283:3, AR252:3, AR171:3, AR162:3, AR180:3, AR163:3, AR243:3, AR217:3, AR161:3, AR176:3, AR165:3, AR213:3, AR282:3, AR164:3, AR291:3, AR296:3, AR245:2, AR235:2, AR089:2, AR263:2, AR231:2, AR246:2, AR297:2, AR313:2, AR224:2, AR172:2, AR195:2, AR174:2, AR286:2, AR168:2, AR060:2, AR289:2, AR201:2, AR294:2, AR177:2, AR300:2, AR225:2, AR211:2, AR179:2, AR229:1, AR240:1, AR205:1, AR239:1, AR285:1, AR299:1, AR257:1, AR264:1, AR212:1, AR166:1, AR316:1, AR287:1, AR227:1, AR247:1, AR270:1, AR170:1, AR216:1, AR096:1, AR237:1, AR104:1 L0766:3, L0777:2, S0116:1, S0376:1, H0457:1, S0440:1, L0771:1, L0803:1, L0804:1, L0657:1, L0659:1, H0525:1, S0406:1 and L0750:1.
55	HEPAB80	1307790	65	AR191:117, AR190:89, AR245:79, AR271:76, AR175:71, AR178:66, AR189:63, AR240:60, AR246:60, AR269:58, AR174:58, AR188:56, AR196:55, AR180:54, AR197:54, AR176:53, AR183:53, AR211:52, AR274:50, AR182:47, AR177:47, AR207:45, AR192:44, AR235:44, AR270:44, AR179:43, AR181:41, AR268:41, AR312:40, AR264:40, AR261:39, AR165:39, AR166:39, AR263:38, AR250:38, AR164:37, AR290:37, AR252:37, AR266:35, AR200:34, AR291:34, AR210:34, AR285:33,

				AR255:32, AR243:32, AR295:31, AR247:30, AR254:29, AR308:28, AR236:28, AR275:28, AR201:28, AR173:28, AR033:27, AR163:26, AR267:26, AR238:26, AR195:25, AR198:25, AR253:25, AR287:25, AR193:25, AR161:24, AR260:24, AR311:24, AR288:23, AR297:23, AR162:21, AR205:21, AR294:21, AR239:20, AR256:20, AR313:20, AR289:20, AR096:20, AR060:20, AR262:19, AR300:18, AR258:18, AR185:18, AR226:17, AR272:17, AR257:17, AR219:17, AR232:16, AR039:16, AR316:16, AR293:15, AR237:15, AR296:15, AR309:15, AR282:14, AR234:14, AR224:14, AR231:13, AR053:13, AR233:13, AR203:13, AR229:13, AR286:12, AR299:12, AR199:12, AR172:11, AR222:11, AR221:11, AR212:11, AR061:11, AR089:11, AR277:10, AR169:10, AR230:10, AR242:10, AR104:10, AR223:10, AR213:9, AR228:9, AR168:9, AR218:9, AR170:8, AR204:8, AR225:8, AR227:7, AR216:6, AR214:6, AR055:5, AR171:5, AR283:5, AR215:3, AR217:2 H0150:1
	HEPAB80	570048	229	
56	HFABH95	566712	66	AR173:16, AR162:14, AR161:14, AR163:13, AR180:12, AR178:11, AR257:11, AR262:11, AR191:11, AR196:10, AR181:10, AR226:10, AR174:10, AR297:10, AR255:9, AR165:9, AR238:9, AR313:9, AR287:8, AR164:8, AR199:8, AR258:8, AR166:8, AR176:8, AR240:8, AR236:8, AR179:8, AR183:8, AR261:8, AR264:7, AR288:7, AR260:7, AR225:7, AR182:7, AR242:7, AR230:7, AR200:7, AR089:7, AR229:7, AR247:7, AR203:7, AR189:7, AR227:7, AR234:6, AR188:6, AR061:6, AR237:6, AR231:6, AR175:6, AR228:6, AR269:6, AR270:6, AR233:6, AR300:6, AR296:6, AR299:6, AR221:5, AR254:5, AR239:5, AR293:5, AR060:5, AR193:5, AR223:5, AR185:5, AR190:5, AR217:5, AR232:5, AR171:5, AR215:5, AR245:5, AR212:5, AR216:5, AR274:5, AR294:5, AR290:5, AR282:4, AR291:4, AR266:4, AR316:4, AR169:4, AR268:4, AR204:4, AR285:4, AR267:4, AR218:4, AR210:4, AR096:4, AR177:4, AR311:4, AR246:4, AR184:4, AR277:4, AR170:4, AR286:4, AR272:4, AR192:4, AR033:4, AR235:4, AR312:4, AR308:4, AR275:3, AR263:3, AR053:3, AR214:3, AR253:3, AR309:3, AR172:3, AR202:3, AR201:3, AR168:3, AR197:3, AR211:3, AR224:3, AR289:3, AR198:3, AR213:3, AR219:3, AR195:3, AR052:3, AR104:3, AR207:3, AR295:2, AR256:2, AR222:2, AR205:2, AR271:2, AR039:2, AR186:2, AR243:2, AR283:2, AR055:2, AR273:2, AR206:1, AR244:1, AR252:1 S6024:1, S0430:1, H0039:1, H0056:1 and H0660:1.
57	HFAEF57	534142	67	AR241:14, AR161:14, AR162:13, AR163:13, AR313:10, AR242:10, AR201:10, AR165:9, AR164:9, AR252:9, AR197:9, AR194:9, AR053:9, AR166:9, AR198:8, AR245:8, AR236:8, AR192:8, AR176:8, AR206:8, AR250:8, AR212:8, AR235:8, AR196:7, AR271:7, AR186:7, AR052:7, AR173:7, AR204:7, AR246:7, AR253:7, AR263:7, AR207:7, AR191:7, AR275:7, AR180:7, AR226:7, AR272:7, AR247:7, AR181:6, AR299:6, AR089:6, AR195:6, AR293:6, AR244:6, AR193:6, AR312:6, AR213:6, AR229:6, AR039:6, AR280:6, AR251:6, AR188:6, AR202:6, AR309:6, AR287:6, AR264:6, AR238:6, AR273:6, AR174:6, AR177:6, AR240:6, AR257:6, AR237:5, AR243:5, AR061:5, AR233:5, AR228:5, AR261:5, AR184:5, AR182:5, AR262:5, AR185:5, AR300:5, AR270:5, AR096:5, AR189:5, AR190:5, AR274:5, AR248:5, AR205:5, AR315:5, AR183:5, AR175:5, AR288:5, AR169:5, AR033:5, AR297:5, AR269:5, AR199:5, AR178:5, AR249:5, AR295:5, AR308:4, AR055:4, AR223:4, AR254:4, AR060:4, AR104:4, AR216:4, AR296:4, AR227:4, AR290:4, AR221:4, AR266:4, AR232:4, AR239:4, AR311:4, AR179:4, AR298:4, AR200:4, AR231:4, AR285:4, AR255:4, AR268:4, AR286:4, AR267:4, AR282:4, AR230:4, AR294:4, AR316:4, AR214:4, AR234:4, AR168:4, AR277:3, AR258:3, AR291:3, AR170:3, AR217:3, AR203:3, AR292:3, AR171:3, AR289:3, AR310:3, AR265:3, AR215:3, AR259:3, AR284:3, AR225:2, AR281:2, AR219:2, AR218:2, AR283:2, AR222:2, AR314:2, AR260:2, AR210:2, AR172:2, AR224:2, AR211:1, AR256:1 S6024:1
58	HFCEB37	411345	68	AR282:18, AR176:14, AR269:13, AR183:11, AR173:11, AR201:11, AR182:11, AR252:11, AR204:11, AR193:11, AR294:10, AR243:9, AR233:9, AR236:9, AR197:9, AR162:9, AR161:9, AR270:9, AR163:9, AR178:9, AR165:9, AR217:9, AR225:9,

				AR175:9, AR231:9, AR181:9, AR089:8, AR215:8, AR164:8, AR207:8, AR170:8, AR216:8, AR166:8, AR172:8, AR268:8, AR221:8, AR291:8, AR169:8, AR179:8, AR261:8, AR235:8, AR205:8, AR224:8, AR039:7, AR180:7, AR060:7, AR242:7, AR267:7, AR228:7, AR168:7, AR223:7, AR290:7, AR198:7, AR296:7, AR266:7, AR285:7, AR287:7, AR316:7, AR174:7, AR257:7, AR237:7, AR271:7, AR245:7, AR313:7, AR033:7, AR229:7, AR192:7, AR255:7, AR250:7, AR288:7, AR191:6, AR254:6, AR096:6, AR177:6, AR055:6, AR195:6, AR246:6, AR238:6, AR222:6, AR240:6, AR239:6, AR262:6, AR293:6, AR247:6, AR300:6, AR289:6, AR264:6, AR214:6, AR299:6, AR188:6, AR297:6, AR190:6, AR171:6, AR253:6, AR200:6, AR295:5, AR053:5, AR185:5, AR226:5, AR196:5, AR309:5, AR274:5, AR312:5, AR234:5, AR189:5, AR286:5, AR061:4, AR308:4, AR227:4, AR275:4, AR104:4, AR263:4, AR258:4, AR218:4, AR203:4, AR232:4, AR272:4, AR230:4, AR277:4, AR256:4, AR212:3, AR199:3, AR210:3, AR211:3, AR311:3, AR283:3, AR219:3, AR213:3, AR260:2 S0222:2, L0438:2, S0134:1, S0045:1, H0747:1, H0013:1, H0009:1, S6028:1, L0598:1, L0532:1, S0052:1, H0696:1, S0146:1, L0439:1, L0777:1 and L0366:1.
59	HFFAD59	520369	69	AR225:3, AR162:3, AR161:3, AR271:3, AR183:2, AR180:2, AR282:2, AR217:2, AR254:2, AR198:2, AR291:2, AR175:2, AR288:2, AR177:2, AR201:2, AR163:2, AR267:2, AR224:2, AR295:2, AR266:2, AR312:2, AR173:2, AR277:2, AR311:2, AR238:2, AR033:2, AR193:2, AR228:2, AR294:2, AR195:2, AR275:1, AR243:1, AR272:1, AR205:1, AR174:1, AR213:1, AR293:1, AR308:1, AR229:1, AR233:1, AR285:1, AR247:1, AR269:1, AR181:1, AR182:1, AR230:1, AR296:1, AR185:1, AR240:1, AR297:1, AR258:1 H0172:2
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61	HFIUR10	532060	71	AR169:4, AR165:4, AR161:3, AR163:3, AR215:3, AR162:3, AR166:3, AR246:3, AR252:3, AR313:3, AR089:3, AR311:3, AR266:2, AR270:2, AR180:2, AR261:2, AR164:2, AR224:2, AR269:2, AR096:2, AR236:2, AR289:2, AR201:2, AR297:2, AR312:2, AR205:2, AR217:2, AR255:2, AR172:2, AR240:2, AR216:2, AR183:2, AR309:2, AR173:2, AR291:2, AR176:2, AR196:2, AR295:1, AR264:1, AR225:1, AR299:1, AR033:1, AR174:1, AR257:1, AR282:1, AR060:1, AR230:1, AR178:1, AR177:1, AR316:1, AR168:1, AR243:1, AR283:1, AR268:1, AR277:1, AR189:1, AR290:1, AR247:1, AR055:1, AR308:1, AR288:1, AR300:1, AR237:1, AR185:1 H0265:2, L0591:2, H0556:1, S0356:1, H0271:1, H0622:1, S0428:1, S0434:1 and S0196:1.

62	HFTBM50	545012	72	AR300:4, AR104:4, AR240:4, AR277:3, AR060:3, AR185:3, AR055:3, AR299:2, AR316:2, AR282:2, AR219:2, AR089:2, AR283:2, AR218:2, AR096:2, AR039:2, AR313:1 L0439:6, L0731:4, L0769:2, L0666:2, S0432:2, S0206:2, L0751:2, L0777:2, L0759:2, L0591:2, H0341:1, H0661:1, S0408:1, H0601:1, H0497:1, H0123:1, L0471:1, H0051:1, H0252:1, H0673:1, H0616:1, H0551:1, H0646:1, S0422:1, L0372:1, L0771:1, L0773:1, L0768:1, L0775:1, L0375:1, L0527:1, L0664:1, L0665:1, S0374:1, H0519:1, H0659:1, H0521:1, H0522:1, L0747:1, L0749:1, L0755:1, L0758:1, S0031:1, L0683:1, L0590:1 and L0595:1.
63	HFTDZ36	545726	73	AR282:5, AR176:3, AR252:2, AR270:2, AR287:2, AR309:2, AR221:2, AR263:2, AR291:2, AR224:2, AR233:2, AR181:2, AR198:2, AR240:2, AR222:2, AR193:2, AR214:2, AR286:2, AR165:2, AR164:1, AR178:1, AR236:1, AR201:1, AR168:1, AR089:1, AR262:1, AR060:1, AR217:1, AR161:1, AR272:1, AR264:1, AR061:1, AR195:1, AR257:1, AR268:1, AR215:1, AR285:1, AR258:1, AR210:1, AR104:1, AR196:1 L0779:5, L0758:4, S0036:2, H0038:2, S0422:2, L0662:2, L0803:2, H0171:1, H0208:1, H0411:1, S0222:1, H0013:1, H0108:1, H0581:1, H0123:1, H0024:1, H0373:1, S0051:1, S6028:1, H0615:1, L0794:1, L0804:1, S0126:1, H0436:1, S0028:1, L0756:1, L0777:1, L0731:1 and S0242:1.
64	HFXBL33	778070	74	AR163:25, AR161:24, AR162:24, AR313:23, AR173:17, AR180:17, AR196:17, AR165:17, AR166:16, AR229:16, AR164:16, AR270:14, AR247:14, AR182:14, AR238:14, AR234:14, AR175:14, AR179:13, AR269:13, AR181:13, AR178:13, AR199:12, AR258:12, AR262:12, AR240:11, AR233:11, AR257:11, AR183:11, AR264:11, AR300:10, AR268:10, AR285:10, AR293:10, AR274:10, AR231:10, AR275:10, AR191:10, AR230:10, AR228:10, AR236:10, AR237:10, AR226:10, AR239:9, AR287:9, AR203:9, AR294:9, AR174:9, AR296:9, AR260:8, AR176:8, AR189:8, AR200:8, AR312:8, AR033:8, AR096:8, AR185:8, AR299:8, AR255:7, AR297:7, AR267:7, AR188:7, AR177:7, AR290:7, AR277:6, AR218:6, AR190:6, AR286:6, AR291:6, AR089:6, AR266:6, AR060:6, AR227:6, AR219:6, AR263:5, AR295:5, AR316:5, AR311:5, AR261:5, AR055:5, AR235:5, AR309:5, AR282:5, AR272:4, AR288:4, AR308:4, AR256:4, AR053:4, AR289:4, AR104:4, AR283:4, AR215:4, AR223:4, AR232:4, AR212:4, AR213:3, AR061:3, AR211:3, AR217:3, AR216:3, AR169:3, AR210:3, AR195:3, AR168:2, AR225:2, AR201:2, AR193:2, AR171:2, AR214:2, AR039:2, AR243:2, AR222:2, AR170:1, AR246:1, AR224:1 H0657:3, H0645:2, L0748:2, H0542:2, H0583:1, H0650:1, S0001:1, L0586:1, H0013:1, L0021:1, T0071:1, H0354:1, H0179:1, T0006:1, H0591:1, H0272:1, L0667:1, H0547:1, H0521:1, S0404:1, S0031:1 and L0599:1.
65	HFXJX44	701988	75	AR313:13, AR162:11, AR161:10, AR178:10, AR163:10, AR176:10, AR183:10, AR165:9, AR089:9, AR181:9, AR182:9, AR164:9, AR229:9, AR166:8, AR269:8, AR173:8, AR196:8, AR055:8, AR300:8, AR228:8, AR175:7, AR233:7, AR226:7, AR309:7, AR247:7, AR192:7, AR239:7, AR180:7, AR236:7, AR257:7, AR293:7, AR266:7, AR235:7, AR240:7, AR238:7, AR267:7, AR096:7, AR177:7, AR261:6, AR053:6, AR179:6, AR245:6, AR268:6, AR282:6, AR299:6, AR198:6, AR290:6, AR204:6, AR191:6, AR060:6, AR262:6, AR174:6, AR277:6, AR312:6, AR271:6, AR185:5, AR316:5, AR289:5, AR270:5, AR294:5, AR193:5, AR201:5, AR258:5, AR296:5, AR212:5, AR237:5, AR255:5, AR227:5, AR234:5, AR061:5, AR274:5, AR275:5, AR264:5, AR197:5, AR287:5, AR243:5, AR297:5, AR286:4, AR263:4, AR199:4, AR200:4, AR231:4, AR203:4, AR291:4, AR214:4, AR242:4, AR285:4, AR230:4, AR033:4, AR189:4, AR213:4, AR188:4, AR195:4, AR288:4, AR246:4, AR295:4, AR224:4, AR252:3, AR104:3, AR250:3, AR272:3, AR218:3, AR219:3, AR190:3, AR308:3, AR222:3, AR171:3, AR260:3, AR207:3, AR168:3, AR205:3, AR283:3, AR232:3, AR039:3, AR311:2, AR172:2, AR256:2, AR221:2, AR225:2, AR217:2, AR169:1, AR210:1, AR211:1, AR254:1 H0590:2, S0282:1, H0486:1, H0421:1 and H0594:1.
66	HFXKT05	658690	76	AR207:65, AR197:54, AR193:47, AR192:45, AR201:42, AR033:40, AR299:40, AR055:39, AR242:38, AR235:38, AR177:38,

				AR233:37, AR198:35, AR185:33, AR060:33, AR195:32, AR174:31, AR203:31, AR191:31, AR204:31, AR061:30, AR104:30, AR181:30, AR243:29, AR179:29, AR257:28, AR165:28, AR196:28, AR176:28, AR190:28, AR089:27, AR175:27, AR213:27, AR291:27, AR164:27, AR228:27, AR288:27, AR287:26, AR275:26, AR161:26, AR166:26, AR238:26, AR236:26, AR163:26, AR199:25, AR178:25, AR245:24, AR162:24, AR267:24, AR226:23, AR039:23, AR246:23, AR261:23, AR205:23, AR173:23, AR286:22, AR250:22, AR240:22, AR296:22, AR316:22, AR247:21, AR293:21, AR232:21, AR231:21, AR188:21, AR294:21, AR053:20, AR255:20, AR289:20, AR282:20, AR189:20, AR212:20, AR300:20, AR230:20, AR295:19, AR239:19, AR270:19, AR258:19, AR234:19, AR308:19, AR269:18, AR180:18, AR253:18, AR285:17, AR227:17, AR297:17, AR254:17, AR272:17, AR237:17, AR200:16, AR182:16, AR271:16, AR262:16, AR277:16, AR312:15, AR229:15, AR260:15, AR263:15, AR274:14, AR268:13, AR266:13, AR309:13, AR096:13, AR290:13, AR264:12, AR183:12, AR252:11, AR313:10, AR311:10, AR256:9, AR225:9, AR283:9, AR211:7, AR172:7, AR210:7, AR223:7, AR224:7, AR171:6, AR217:6, AR221:6, AR216:5, AR219:5, AR170:5, AR215:5, AR222:4, AR214:4, AR168:3, AR218:3, AR169:3 L2804:16, L2400:15, L0748:8, L3019:5, L3316:3, L2138:3, H0553:2, L3140:2, L3904:2, S0378:2, L0777:2, L0758:2, H0657:1, S0282:1, H0402:1, L0005:1, H0333:1, T0114:1, S0280:1, H0618:1, H0253:1, H0581:1, H0052:1, H0050:1, H0620:1, S0388:1, H0354:1, H0135:1, S0344:1, L0763:1, L0638:1, L0761:1, L0764:1, L0363:1, L0766:1, L0651:1, L0805:1, L0655:1, L0659:1, L0666:1, L2261:1, H0701:1, L0749:1, L0756:1, L0779:1, L0752:1, L0599:1, H0542:1, H0423:1, H0422:1 and H0506:1.
67	HGBHI35	570262	77	AR089:24, AR226:21, AR299:20, AR164:20, AR165:20, AR060:19, AR166:17, AR185:16, AR201:16, AR163:15, AR161:15, AR162:15, AR232:15, AR096:14, AR188:14, AR237:14, AR039:14, AR227:14, AR233:13, AR238:13, AR275:12, AR193:12, AR191:12, AR055:12, AR173:11, AR246:11, AR183:11, AR240:11, AR228:11, AR196:11, AR316:11, AR313:11, AR189:10, AR239:10, AR061:10, AR175:10, AR258:10, AR199:10, AR176:10, AR180:10, AR197:9, AR190:9, AR174:9, AR283:9, AR270:9, AR266:9, AR245:9, AR203:9, AR231:9, AR195:9, AR300:8, AR257:8, AR269:8, AR169:8, AR178:8, AR242:8, AR182:8, AR277:8, AR234:8, AR192:8, AR236:8, AR235:8, AR297:8, AR291:8, AR198:8, AR181:8, AR282:8, AR295:8, AR264:8, AR218:8, AR274:7, AR294:7, AR217:7, AR177:7, AR285:7, AR247:7, AR271:7, AR263:7, AR288:7, AR104:7, AR219:7, AR229:7, AR261:7, AR215:7, AR216:6, AR287:6, AR286:6, AR255:6, AR179:6, AR268:6, AR243:6, AR262:6, AR205:6, AR289:6, AR293:6, AR223:6, AR267:5, AR200:5, AR312:5, AR254:5, AR290:5, AR260:5, AR308:5, AR311:5, AR309:5, AR204:5, AR230:5, AR296:4, AR213:4, AR225:4, AR170:4, AR272:4, AR252:4, AR256:4, AR214:4, AR222:3, AR207:3, AR053:3, AR211:3, AR172:3, AR210:3, AR033:2, AR212:2, AR224:2, AR171:2, AR168:2 L0748:9, L0766:6, L0665:6, L0751:6, H0550:5, S0358:4, L0774:4, L0758:4, L0581:4, H0135:3, L0662:3, L0775:3, L0776:3, L0743:3, L0747:3, L0749:3, L0777:3, L0600:3, H0295:2, H0722:2, H0052:2, H0014:2, H0510:2, L0640:2, L0659:2, L0526:2, L0809:2, H0696:2, L0753:2, S0134:1, S0212:1, S0376:1, S0408:1, H0742:1, H0730:1, H0747:1, H0549:1, H0331:1, H0486:1, H0575:1, S0049:1, H0085:1, H0204:1, H0057:1, S0051:1, H0266:1, H0188:1, H0687:1, H0169:1, H0090:1, H0591:1, T0067:1, H0488:1, H0714:1, S0438:1, L0374:1, L0648:1, L0376:1, L0807:1, L5622:1, L0790:1, L0791:1, L0666:1, H0701:1, H0547:1, S0126:1, H0660:1, H0672:1, H0539:1, H0436:1, L0439:1, L0746:1, L0750:1, L0779:1, L0752:1, L0759:1 and S0436:1.
68	HGLAF75	566838	78	AR196:8, AR191:7, AR269:7, AR215:7, AR180:6, AR188:6, AR270:6, AR223:6, AR173:6, AR198:5, AR176:5, AR178:5, AR268:5, AR055:5, AR165:5, AR175:5, AR181:5, AR266:5, AR161:5, AR162:5, AR264:5, AR183:5, AR060:5, AR174:5, AR164:5, AR291:5, AR163:5, AR172:5, AR182:5, AR189:5, AR201:5, AR166:5, AR261:5, AR089:5, AR313:5, AR193:5, AR177:4, AR246:4, AR255:4, AR216:4, AR285:4, AR179:4, AR257:4, AR217:4, AR170:4, AR221:4, AR290:4, AR299:4,

				AR252:4, AR200:4, AR267:4, AR262:4, AR235:4, AR185:4, AR240:4, AR238:4, AR233:4, AR295:4, AR316:4, AR168:4, AR190:4, AR218:4, AR271:4, AR236:4, AR296:4, AR096:4, AR287:4, AR199:4, AR293:4, AR272:4, AR242:4, AR297:4, AR243:4, AR294:4, AR195:4, AR300:4, AR169:3, AR224:3, AR253:3, AR282:3, AR203:3, AR239:3, AR033:3, AR288:3, AR309:3, AR171:3, AR222:3, AR211:3, AR312:3, AR275:3, AR231:3, AR232:3, AR192:3, AR247:3, AR260:3, AR228:3, AR104:3, AR283:3, AR229:3, AR210:3, AR225:3, AR039:3, AR258:3, AR205:3, AR234:3, AR286:3, AR289:3, AR308:3, AR230:3, AR263:3, AR219:3, AR237:3, AR214:3, AR277:2, AR204:2, AR227:2, AR274:2, AR256:2, AR226:2, AR061:2, AR245:2, AR212:2, AR213:2, AR311:1 H0351:10, L0439:4, L0766:3, L3255:2, L2562:2, L0775:2, L0666:2, L0779:2, L0780:2, L0755:2, L0731:2, H0772:1, L3388:1, H0333:1, H0486:1, H0015:1, H0687:1, S0422:1, L0761:1, L0776:1, L0659:1, L0663:1, H0682:1, S0152:1, L0745:1, L0752:1 and S0026:1.
69	HHENV10	562772	79	AR242:3, AR235:3, AR183:3, AR309:3, AR282:3, AR243:2, AR171:2, AR283:1, AR055:1, AR257:1, AR168:1, AR213:1, AR164:1, AR230:1, AR264:1, AR287:1 H0543:2, H0497:1 and H0625:1.
70	HHGCG53	340818	80	AR192:3, AR169:3, AR264:3, AR162:3, AR309:3, AR245:3, AR250:3, AR161:3, AR163:3, AR171:3, AR193:2, AR266:2, AR176:2, AR289:2, AR283:2, AR267:2, AR197:2, AR274:2, AR242:2, AR239:2, AR295:2, AR238:2, AR225:2, AR182:2, AR263:2, AR261:2, AR183:2, AR172:1, AR269:1, AR168:1, AR231:1, AR216:1, AR237:1, AR164:1, AR228:1, AR096:1, AR215:1, AR233:1, AR252:1, AR166:1, AR232:1, AR060:1, AR277:1, AR089:1, AR290:1, AR299:1, AR240:1, AR229:1, AR282:1, AR296:1 H0333:1
71	HHGCM76	662329	81	AR245:8, AR175:7, AR183:6, AR176:6, AR196:6, AR191:6, AR174:6, AR060:5, AR254:5, AR263:5, AR039:5, AR173:5, AR177:5, AR309:5, AR261:5, AR232:4, AR161:4, AR162:4, AR096:4, AR163:4, AR182:4, AR264:4, AR089:4, AR165:4, AR198:4, AR270:4, AR275:4, AR268:4, AR178:4, AR189:4, AR164:4, AR166:3, AR286:3, AR242:3, AR193:3, AR243:3, AR216:3, AR171:3, AR283:3, AR266:3, AR215:3, AR272:3, AR211:3, AR188:3, AR313:3, AR180:3, AR207:3, AR269:3, AR200:3, AR247:3, AR316:3, AR289:3, AR290:3, AR229:3, AR294:3, AR297:3, AR195:3, AR267:3, AR061:3, AR240:3, AR295:3, AR197:3, AR238:3, AR257:3, AR190:3, AR055:3, AR228:2, AR181:2, AR053:2, AR033:2, AR288:2, AR226:2, AR282:2, AR201:2, AR239:2, AR287:2, AR231:2, AR262:2, AR223:2, AR104:2, AR285:2, AR308:2, AR218:2, AR179:2, AR293:2, AR221:2, AR311:2, AR271:2, AR225:2, AR246:2, AR185:2, AR237:2, AR299:2, AR312:2, AR274:2, AR233:2, AR199:2, AR227:2, AR219:2, AR300:2, AR213:2, AR256:2, AR296:2, AR234:2, AR291:2, AR172:2, AR205:2, AR252:2, AR230:1, AR203:1, AR255:1, AR214:1, AR258:1, AR224:1, AR260:1, AR277:1, AR210:1 L0803:6, H0052:4, H0036:3, L0665:3, H0574:2, H0559:2, L0763:2, L0809:2, L0791:2, L0666:2, L0663:2, L0748:2, L0745:2, L0747:2, H0624:1, H0265:1, H0657:1, H0381:1, S0045:1, H0550:1, H0614:1, H0587:1, H0333:1, T0040:1, L0022:1, H0575:1, H0564:1, H0068:1, H0509:1, L0769:1, L0637:1, L0643:1, L0764:1, L0662:1, L0804:1, L0806:1, L0527:1, L0783:1, L0382:1, L0664:1, H0144:1, H0690:1, H0682:1, H0670:1, H0694:1, H0626:1, L0743:1, L0777:1, L0780:1, L0755:1, H0343:1 and S0011:1.
	HHGCM76	383547	230	
72	HHPEN62	695134	82	AR196:528, AR310:360, AR218:326, AR052:317, AR219:315, AR194:272, AR211:264, AR206:250, AR202:237, AR205:232, AR265:232, AR244:224, AR053:218, AR184:208, AR246:207, AR241:203, AR284:198, AR309:192, AR186:185, AR263:184, AR273:173, AR280:170, AR298:170, AR243:168, AR247:157, AR315:155, AR312:152, AR311:150, AR314:145, AR281:140, AR039:139, AR182:139, AR275:137, AR271:130, AR313:130, AR185:128, AR177:121, AR213:121, AR204:120, AR104:118, AR300:116, AR274:115, AR210:115, AR245:112, AR229:112,

				AR240:112, AR299:112, AR055:112, AR308:112, AR061:112, AR207:109, AR096:108, AR290:107, AR237:107, AR316:106, AR248:104, AR264:100, AR193:99, AR198:99, AR292:99, AR268:96, AR033:95, AR249:94, AR231:94, AR197:94, AR188:94, AR259:93, AR233:92, AR222:92, AR179:90, AR251:88, AR192:88, AR227:87, AR267:86, AR269:84, AR232:84, AR195:82, AR060:81, AR200:80, AR270:80, AR223:80, AR272:79, AR089:77, AR172:76, AR175:76, AR253:74, AR250:74, AR234:74, AR282:72, AR212:70, AR242:69, AR201:67, AR199:66, AR176:66, AR180:64, AR294:64, AR178:64, AR189:62, AR181:60, AR289:59, AR283:59, AR291:58, AR169:57, AR285:56, AR171:55, AR226:55, AR236:54, AR183:53, AR256:52, AR266:50, AR174:50, AR295:49, AR293:49, AR191:47, AR173:47, AR286:47, AR190:47, AR254:46, AR221:46, AR225:46, AR238:45, AR170:43, AR258:42, AR163:41, AR224:39, AR235:39, AR277:39, AR168:38, AR296:37, AR203:37, AR166:34, AR161:34, AR262:34, AR164:32, AR162:32, AR165:31, AR255:30, AR288:28, AR261:25, AR260:20, AR217:20, AR230:17, AR297:15, AR252:15, AR287:15, AR214:14, AR228:13, AR239:12, AR216:12, AR215:11, AR257:11 L0766:7, L0731:7, H0457:6, H0051:6, L0754:6, L0803:4, L0666:4, H0140:3, S0474:3, H0052:3, L0157:3, L0662:3, L0659:3, L5622:3, L0758:3, H0657:2, S0140:2, S0010:2, H0628:2, S0036:2, H0100:2, S0112:2, L0532:2, L0438:2, H0547:2, L0743:2, S0242:2, H0542:2, H0422:2, H0265:1, H0656:1, S0282:1, S0444:1, S0360:1, S0408:1, H0735:1, H0749:1, L0463:1, H0351:1, H0261:1, H0438:1, H0586:1, H0635:1, H0599:1, H0318:1, H0581:1, H0251:1, H0327:1, H0545:1, H0046:1, L0471:1, S0051:1, H0375:1, H0622:1, T0006:1, H0553:1, H0598:1, H0163:1, H0040:1, H0551:1, L0564:1, H0334:1, H0561:1, S0440:1, H0529:1, L0800:1, L0794:1, L0651:1, L0805:1, L0655:1, L0606:1, L0527:1, L0635:1, L0382:1, L0809:1, L0792:1, L0663:1, S0216:1, H0144:1, H0520:1, H0519:1, S0328:1, S0380:1, S0404:1, H0436:1, S0392:1, S0028:1, L0745:1, L0779:1, L0777:1, L0752:1, S0260:1, L0480:1, S0026:1, H0665:1, S0192:1, S0194:1, H0423:1, S0424:1 and H0506:1.
73	HJABB94	456466	83	AR176:9, AR225:9, AR221:8, AR295:8, AR170:8, AR264:8, AR178:8, AR288:7, AR291:7, AR180:7, AR215:7, AR175:7, AR275:7, AR297:7, AR224:7, AR268:7, AR293:7, AR228:7, AR269:6, AR309:6, AR270:6, AR263:6, AR285:6, AR296:6, AR267:6, AR282:6, AR162:6, AR239:6, AR173:6, AR311:6, AR161:5, AR231:5, AR266:5, AR181:5, AR207:5, AR182:5, AR163:5, AR183:5, AR053:5, AR238:5, AR289:5, AR217:5, AR213:5, AR229:5, AR274:5, AR286:5, AR177:5, AR290:5, AR237:5, AR287:5, AR033:5, AR226:5, AR294:5, AR277:5, AR196:5, AR212:4, AR179:4, AR235:4, AR216:4, AR055:4, AR223:4, AR233:4, AR260:4, AR316:4, AR211:4, AR283:4, AR171:4, AR312:4, AR192:4, AR256:4, AR227:4, AR261:4, AR190:4, AR230:4, AR104:4, AR300:4, AR240:4, AR060:4, AR174:4, AR169:3, AR198:3, AR222:3, AR218:3, AR191:3, AR199:3, AR210:3, AR189:3, AR271:3, AR195:3, AR313:3, AR219:3, AR039:3, AR232:3, AR188:3, AR096:3, AR089:3, AR185:3, AR200:3, AR172:3, AR166:3, AR234:3, AR168:3, AR165:3, AR164:3, AR258:3, AR257:3, AR299:3, AR308:2, AR201:2, AR243:2, AR193:2, AR203:2, AR061:2, AR247:2, AR255:2, AR262:2, AR272:2, AR236:2, AR242:1, AR254:1 H0624:1, S0360:1, H0586:1, L0021:1, T0041:1 and L0779:1.
74	HJACG30	895505	84	AR263:8, AR165:8, AR250:8, AR162:7, AR161:7, AR205:7, AR196:7, AR166:7, AR164:7, AR215:7, AR163:7, AR192:7, AR198:7, AR235:7, AR245:6, AR264:6, AR216:6, AR270:6, AR207:6, AR309:6, AR246:6, AR174:5, AR223:5, AR269:5, AR168:5, AR243:5, AR224:5, AR180:5, AR311:5, AR183:5, AR308:5, AR254:5, AR173:5, AR177:5, AR268:5, AR242:5, AR179:5, AR312:5, AR176:5, AR175:5, AR291:5, AR221:5, AR181:5, AR285:4, AR170:4, AR275:4, AR295:4, AR053:4, AR271:4, AR191:4, AR288:4, AR204:4, AR316:4, AR274:4, AR199:4, AR055:4, AR266:4, AR210:4, AR236:4, AR217:4, AR240:4, AR188:4, AR189:4, AR257:4, AR247:4, AR213:4, AR178:4, AR039:4, AR222:4, AR225:4, AR182:4, AR297:4, AR201:4, AR212:4, AR252:4, AR296:4, AR261:4, AR286:3, AR253:3, AR060:3, AR294:3, AR237:3, AR282:3, AR267:3,

				AR262:3, AR290:3, AR172:3, AR171:3, AR287:3, AR299:3, AR231:3, AR289:3, AR197:3, AR193:3, AR293:3, AR255:3, AR190:3, AR200:3, AR228:3, AR033:3, AR313:3, AR211:3, AR258:3, AR300:3, AR089:3, AR238:3, AR185:3, AR233:3, AR229:3, AR277:3, AR226:3, AR239:3, AR230:3, AR234:2, AR214:2, AR260:2, AR096:2, AR061:2, AR195:2, AR219:2, AR203:2, AR256:2, AR272:2, AR232:2, AR227:2, AR218:1, AR283:1, AR104:1, AR169:1 H0069:3, T0041:2, H0436:2, H0318:1, L4747:1, L0646:1, L0766:1 and L0803:1.
	HJACG30	821341	231	
	HJACG30	774300	232	
75	HJBCY35	719729	85	AR215:11, AR291:11, AR225:10, AR217:9, AR216:8, AR296:8, AR214:8, AR297:8, AR266:7, AR183:7, AR257:7, AR223:7, AR170:7, AR269:7, AR287:7, AR221:6, AR270:6, AR171:6, AR182:6, AR286:6, AR169:6, AR172:6, AR294:6, AR176:6, AR235:6, AR163:5, AR295:5, AR161:5, AR168:5, AR255:5, AR162:5, AR224:5, AR285:5, AR293:5, AR268:5, AR289:5, AR288:5, AR263:5, AR264:5, AR165:4, AR173:4, AR260:4, AR262:4, AR175:4, AR164:4, AR179:4, AR055:4, AR104:4, AR222:4, AR166:4, AR060:4, AR181:4, AR242:4, AR313:4, AR283:4, AR258:4, AR240:4, AR311:4, AR290:3, AR180:3, AR282:3, AR247:3, AR231:3, AR316:3, AR267:3, AR233:3, AR228:3, AR300:3, AR236:3, AR177:3, AR096:3, AR212:3, AR256:3, AR275:3, AR237:3, AR185:3, AR239:3, AR299:3, AR245:3, AR229:3, AR039:3, AR238:3, AR234:3, AR191:3, AR190:2, AR199:2, AR089:2, AR178:2, AR277:2, AR189:2, AR174:2, AR205:2, AR309:2, AR061:2, AR274:2, AR227:2, AR261:2, AR188:2, AR218:2, AR272:2, AR219:2, AR312:2, AR196:2, AR195:2, AR232:2, AR200:2, AR211:2, AR230:2, AR203:1, AR210:1, AR226:1, AR033:1, AR252:1 H0618:16, H0617:13, H0253:11, H0457:6, L0766:6, L0769:5, H0255:4, H0559:4, H0181:4, L0748:4, H0170:3, S0051:3, H0622:3, L0770:3, L0653:3, L0743:3, L0779:3, H0341:2, H0484:2, S0049:2, H0620:2, H0424:2, H0135:2, H0040:2, H0059:2, H0100:2, T0042:2, S0002:2, L0758:2, L0588:2, H0171:1, S0134:1, H0650:1, H0657:1, H0656:1, S0116:1, L0534:1, H0637:1, S6026:1, S0300:1, L0717:1, H0549:1, H0550:1, S6014:1, H0333:1, L2504:1, L2522:1, H0427:1, L0021:1, H0599:1, H0545:1, H0150:1, L0157:1, S0050:1, H0355:1, H0252:1, L0483:1, H0068:1, S0036:1, H0038:1, H0087:1, H0272:1, H0623:1, T0041:1, L4747:1, L3904:1, L3905:1, L0761:1, L0645:1, L0648:1, L0662:1, L0768:1, L0774:1, L0776:1, L0658:1, L4669:1, L0659:1, L0382:1, L0665:1, L2257:1, L2260:1, H0547:1, H0711:1, H0670:1, H0672:1, S0350:1, H0696:1, H0704:1, L0744:1, L0439:1, L0749:1, L0777:1, L0780:1, L0731:1, L0757:1, S0436:1, S0276:1 and H0543:1.
76	HJPAD75	651337	86	AR277:7, AR215:2, AR282:2, AR246:2, AR225:2, AR290:2, AR213:2, AR172:2, AR261:1, AR266:1, AR162:1, AR165:1, AR257:1, AR230:1, AR168:1, AR182:1, AR166:1, AR252:1, AR196:1, AR295:1, AR270:1, AR177:1, AR285:1, AR195:1, AR291:1, AR217:1, AR161:1, AR256:1 H0556:6, L0769:4, L0771:4, H0265:3, L0764:3, H0083:2, S0142:2, L0794:2, L0803:2, L0789:2, L0792:2, L0438:2, L0754:2, L0747:2, L0749:2, L0757:2, S0356:1, S0444:1, S0360:1, H0013:1, S0010:1, H0421:1, H0263:1, H0596:1, L0157:1, L0471:1, H0553:1, H0628:1, H0090:1, H0561:1, S0372:1, L2270:1, S0422:1, L0667:1, L0768:1, L0776:1, L0809:1, H0658:1, H0648:1, S0330:1, H0521:1, H0134:1, S0027:1, L0748:1, L0756:1, L0755:1, L0731:1, S0434:1, L0592:1 and H0542:1.
77	HKABZ65	862030	87	AR313:41, AR242:32, AR039:28, AR165:25, AR163:25, AR164:24, AR161:24, AR162:24, AR166:24, AR089:24, AR096:23, AR173:22, AR196:20, AR193:20, AR299:20, AR300:20, AR258:20, AR180:19, AR175:19, AR178:18, AR240:18, AR229:18, AR234:18, AR185:17, AR247:17, AR218:17, AR262:17, AR179:16, AR285:16, AR183:16, AR269:16, AR293:15, AR174:15, AR199:15, AR182:15, AR181:15, AR238:14, AR191:14, AR296:14, AR236:14, AR257:14, AR316:14, AR270:14, AR226:13,

				AR219:13, AR297:13, AR277:13, AR264:12, AR200:12, AR312:12, AR195:12, AR213:12, AR192:12, AR203:12, AR268:12, AR212:12, AR294:12, AR286:11, AR060:11, AR230:11, AR177:11, AR189:11, AR233:11, AR260:10, AR231:10, AR198:10, AR290:10, AR188:10, AR204:10, AR053:9, AR287:9, AR288:9, AR255:9, AR295:9, AR033:9, AR261:9, AR282:9, AR104:9, AR245:9, AR243:9, AR235:9, AR228:8, AR308:8, AR263:8, AR275:8, AR291:8, AR201:8, AR274:8, AR237:7, AR197:7, AR239:7, AR224:7, AR311:7, AR176:7, AR267:7, AR172:7, AR256:7, AR223:7, AR205:7, AR171:6, AR227:6, AR168:6, AR214:6, AR207:6, AR169:6, AR225:6, AR252:6, AR250:6, AR271:6, AR215:6, AR170:6, AR211:6, AR221:6, AR309:5, AR283:5, AR266:5, AR254:5, AR222:5, AR190:5, AR210:5, AR216:5, AR217:5, AR232:5, AR055:5, AR289:4, AR253:4, AR246:4, AR272:3, AR061:2 H0494:1
	HKABZ65	665424	233	
78	HKACB56	554616	88	AR223:8, AR235:8, AR263:7, AR222:7, AR170:7, AR221:7, AR207:7, AR216:7, AR169:7, AR224:7, AR168:7, AR171:7, AR311:7, AR198:7, AR309:7, AR214:6, AR225:6, AR053:6, AR197:6, AR212:6, AR215:6, AR089:6, AR264:6, AR245:6, AR205:5, AR217:5, AR165:5, AR163:5, AR161:5, AR162:5, AR164:5, AR166:5, AR275:5, AR308:5, AR213:5, AR172:5, AR312:4, AR277:4, AR274:4, AR246:4, AR196:4, AR060:4, AR271:4, AR282:4, AR195:4, AR295:4, AR261:4, AR269:4, AR230:4, AR316:4, AR181:4, AR288:4, AR176:4, AR055:3, AR240:3, AR204:3, AR297:3, AR283:3, AR313:3, AR177:3, AR210:3, AR285:3, AR242:3, AR296:3, AR039:3, AR199:3, AR096:3, AR173:3, AR272:3, AR236:3, AR200:3, AR252:3, AR254:3, AR238:3, AR175:3, AR291:3, AR193:3, AR299:3, AR247:3, AR191:3, AR033:3, AR188:3, AR286:3, AR289:3, AR300:3, AR185:3, AR201:3, AR174:3, AR270:3, AR262:3, AR237:2, AR293:2, AR104:2, AR232:2, AR287:2, AR294:2, AR178:2, AR189:2, AR229:2, AR234:2, AR226:2, AR239:2, AR061:2, AR182:2, AR290:2, AR203:2, AR227:2, AR255:2, AR183:2, AR190:2, AR233:2, AR211:2, AR231:2, AR257:2, AR267:2, AR228:2, AR243:2, AR258:2, AR256:2, AR179:1, AR218:1, AR268:1, AR219:1, AR192:1, AR180:1, AR253:1 H0494:4, L0045:1 and L0806:1.
79	HKACD58	1352202	89	AR261:30, AR235:29, AR283:29, AR297:20, AR291:17, AR285:16, AR286:15, AR295:13, AR183:13, AR269:13, AR287:12, AR258:11, AR268:11, AR266:11, AR289:10, AR161:10, AR162:10, AR288:10, AR236:10, AR260:10, AR165:10, AR163:10, AR166:9, AR207:9, AR164:9, AR270:9, AR282:9, AR277:8, AR223:8, AR214:8, AR243:8, AR215:8, AR224:8, AR296:8, AR096:8, AR039:8, AR172:8, AR221:8, AR192:8, AR316:8, AR182:8, AR104:8, AR089:8, AR222:8, AR293:7, AR173:7, AR176:7, AR255:7, AR169:7, AR171:7, AR311:7, AR257:7, AR313:7, AR225:7, AR245:7, AR254:7, AR180:7, AR211:7, AR262:7, AR195:7, AR290:6, AR240:6, AR175:6, AR179:6, AR217:6, AR247:6, AR256:6, AR055:6, AR309:6, AR168:6, AR300:6, AR294:6, AR197:6, AR219:6, AR263:6, AR299:6, AR242:6, AR216:6, AR060:5, AR238:5, AR267:5, AR185:5, AR250:5, AR264:5, AR181:5, AR234:5, AR053:5, AR199:5, AR275:5, AR178:5, AR308:5, AR033:5, AR274:5, AR193:5, AR177:5, AR218:5, AR174:4, AR213:4, AR170:4, AR246:4, AR212:4, AR312:4, AR198:4, AR253:4, AR205:4, AR271:4, AR189:4, AR191:4, AR210:4, AR201:4, AR239:3, AR237:3, AR252:3, AR196:3, AR190:3, AR233:3, AR231:3, AR227:3, AR061:3, AR226:3, AR230:3, AR272:3, AR229:3, AR204:3, AR232:3, AR203:3, AR200:3, AR188:2, AR228:2 S0360:12, S0436:3, S0194:3, S0114:2, H0483:2, S0408:2, L3504:2, H0575:2, H0581:2, S0344:2, L2262:2, H0519:2, L0754:2, H0139:1, L2884:1, H0657:1, H0656:1, S0420:1, S0356:1, S0410:1, L2333:1, H0151:1, S0046:1, L3127:1, H0549:1, H0613:1, H0427:1, H0546:1, H0081:1, H0355:1, S0312:1, H0032:1, H0383:1, H0551:1, H0264:1, T0042:1, H0494:1, H0386:1, H0509:1, H0649:1, S0210:1, L0646:1, L0804:1, L0805:1, L0809:1, L5622:1, L2651:1, L2265:1, L2702:1, H0682:1, H0435:1, H0670:1, H0672:1, H0521:1, H0696:1, H0134:1, S0206:1, L0741:1, L0743:1, L0744:1, L0756:1, L0596:1, L0581:1, L0593:1, L0595:1,

				L0366:1, S0242:1, S0196:1, H0423:1 and H0506:1.
	HKACD58	552465	234	
80	HKAEV06	1352263	90	AR272:35, AR165:34, AR163:33, AR164:33, AR161:32, AR162:32, AR245:32, AR166:32, AR274:28, AR212:28, AR205:26, AR311:23, AR242:22, AR264:21, AR308:20, AR214:20, AR174:19, AR197:19, AR216:16, AR223:15, AR222:15, AR313:15, AR213:14, AR171:14, AR312:14, AR195:14, AR225:14, AR247:13, AR201:13, AR254:12, AR309:12, AR053:12, AR275:12, AR263:12, AR168:12, AR246:11, AR217:11, AR224:11, AR215:11, AR252:11, AR089:11, AR170:10, AR243:10, AR172:10, AR192:10, AR221:9, AR241:9, AR189:9, AR185:9, AR250:9, AR240:8, AR039:8, AR199:8, AR204:8, AR179:7, AR198:7, AR169:7, AR096:7, AR193:7, AR177:7, AR188:7, AR297:6, AR253:6, AR236:6, AR249:6, AR300:6, AR262:6, AR271:6, AR277:6, AR183:6, AR104:6, AR261:6, AR299:6, AR234:5, AR239:5, AR194:5, AR173:5, AR181:5, AR265:5, AR257:5, AR316:5, AR288:5, AR207:5, AR190:5, AR060:5, AR282:5, AR180:5, AR233:5, AR230:4, AR231:4, AR293:4, AR176:4, AR178:4, AR290:4, AR287:4, AR191:4, AR196:4, AR291:4, AR238:4, AR255:4, AR296:4, AR235:4, AR273:4, AR289:3, AR270:3, AR266:3, AR052:3, AR203:3, AR229:3, AR200:3, AR206:3, AR228:3, AR294:3, AR283:3, AR295:3, AR033:3, AR175:2, AR269:2, AR268:2, AR248:2, AR210:2, AR237:2, AR182:2, AR285:2, AR258:2, AR286:2, AR186:2, AR267:2, AR061:2, AR232:2, AR226:2, AR244:2, AR260:2, AR219:1, AR055:1, AR227:1, AR211:1, AR310:1, AR281:1, AR218:1, AR256:1 L0438:2, L0758:2, S0442:1, S0354:1, S0444:1, H0741:1, L0021:1, T0082:1, H0046:1, H0494:1, S0440:1, L3815:1, L0800:1, L0662:1, L5574:1, L0803:1, L0776:1, L0659:1, L2655:1, L2653:1, S0374:1, H0547:1, H0672:1, S0330:1, H0521:1, H0696:1, L0439:1, L0752:1, L0594:1 and H0543:1.
	HKAEV06	638238	235	
81	HKAFT66	946512	91	AR214:32, AR195:28, AR222:28, AR169:27, AR223:26, AR224:25, AR168:23, AR172:23, AR235:22, AR217:21, AR311:20, AR216:20, AR207:19, AR221:19, AR171:18, AR263:18, AR225:17, AR264:16, AR215:15, AR281:15, AR196:14, AR170:14, AR212:14, AR261:13, AR252:13, AR163:13, AR288:12, AR265:12, AR161:12, AR162:12, AR242:12, AR309:12, AR211:11, AR165:11, AR166:11, AR236:11, AR164:11, AR199:11, AR308:11, AR315:11, AR210:10, AR254:10, AR193:10, AR213:10, AR174:10, AR245:9, AR191:9, AR297:9, AR053:9, AR188:9, AR197:9, AR181:9, AR280:8, AR173:8, AR200:8, AR180:8, AR240:8, AR310:8, AR189:8, AR287:8, AR239:8, AR272:7, AR251:7, AR295:7, AR262:7, AR177:7, AR314:7, AR312:7, AR190:7, AR230:7, AR033:7, AR271:7, AR282:6, AR229:6, AR283:6, AR257:6, AR192:6, AR198:6, AR275:6, AR205:6, AR201:6, AR203:6, AR313:6, AR249:6, AR274:6, AR300:6, AR260:6, AR089:5, AR277:5, AR238:5, AR176:5, AR299:5, AR246:5, AR285:5, AR178:5, AR218:5, AR316:5, AR286:5, AR258:5, AR247:4, AR291:4, AR255:4, AR248:4, AR060:4, AR052:4, AR231:4, AR270:4, AR226:4, AR289:4, AR228:4, AR253:4, AR096:4, AR175:4, AR185:4, AR234:4, AR269:4, AR055:4, AR227:4, AR183:3, AR232:3, AR039:3, AR219:3, AR296:3, AR179:3, AR237:3, AR256:3, AR104:3, AR290:3, AR233:3, AR204:3, AR293:3, AR250:3, AR268:3, AR243:2, AR266:2, AR267:2, AR061:2, AR294:2, AR182:2, AR202:2, AR273:1, AR186:1 S0474:5, S0422:3, H0580:2, S0444:1, H0494:1 and H0543:1.
	HKAFT66	889258	236	
	HKAFT66	904790	237	
82	HKB1E57	876571	92	AR253:4, AR225:3, AR171:3, AR205:3, AR192:3, AR169:3, AR245:2, AR282:2, AR193:2, AR274:2, AR039:2, AR291:2, AR212:2, AR163:2, AR162:2, AR266:2, AR161:2, AR269:2, AR264:1, AR271:1, AR178:1, AR316:1, AR275:1, AR261:1,

				AR168:1, AR270:1, AR183:1, AR297:1, AR283:1 L0747:4, L0766:3, L0776:3, L0665:3, H0328:2, L0763:2, L0769:2, L0772:2, L0764:2, L0666:2, L0745:2, L0750:2, L0777:2, L0759:2, L0608:2, H0556:1, S0116:1, H0384:1, S0360:1, S0408:1, H0637:1, H0722:1, H0735:1, H0619:1, H0492:1, H0156:1, H0421:1, H0620:1, S0051:1, H0083:1, H0510:1, H0266:1, H0031:1, H0634:1, H0560:1, S0440:1, H0132:1, H0695:1, L0800:1, L0521:1, L0662:1, L0774:1, L0806:1, L0807:1, H0144:1, H0690:1, H0658:1, H0521:1, H0522:1, L0439:1, L0746:1, L0752:1, L0480:1, L0589:1, L0592:1, H0543:1 and H0422:1.
	HKB1E57	654871	238	
83	HKFBC53	1352286	93	AR249:155, AR248:131, AR251:111, AR265:54, AR253:42, AR096:23, AR263:23, AR244:18, AR290:13, AR268:13, AR246:12, AR184:11, AR177:11, AR194:9, AR267:8, AR229:8, AR270:8, AR247:7, AR240:7, AR269:7, AR183:6, AR202:5, AR175:5, AR234:5, AR241:5, AR316:5, AR206:5, AR313:5, AR055:4, AR299:4, AR033:4, AR238:3, AR292:3, AR061:3, AR182:3, AR171:3, AR273:3, AR224:3, AR274:3, AR198:3, AR275:3, AR216:3, AR266:3, AR195:3, AR284:3, AR168:3, AR237:2, AR215:2, AR282:2, AR285:2, AR242:2, AR310:2, AR250:2, AR300:2, AR298:2, AR186:2, AR039:2, AR231:2, AR291:2, AR223:2, AR243:2, AR289:2, AR179:2, AR204:2, AR104:2, AR205:2, AR257:2, AR271:2, AR053:2, AR226:2, AR277:2, AR217:2, AR232:2, AR192:2, AR296:2, AR185:2, AR264:1, AR295:1, AR089:1, AR261:1, AR213:1, AR259:1, AR166:1, AR286:1, AR308:1, AR233:1, AR201:1 L0794:11, H0521:11, S0002:8, L0805:8, L0803:7, S0278:6, S0144:6, L0774:4, L0777:4, S0380:3, H0265:2, H0556:2, H0255:2, H0638:2, L0761:2, L0776:2, L0809:2, S0406:2, S0298:1, S0420:1, S0356:1, H0431:1, H0618:1, H0546:1, H0100:1, H0429:1, H0494:1, H0509:1, S0142:1, S0426:1, L0640:1, L0763:1, L0770:1, L3904:1, L0800:1, L0804:1, L0806:1, L0807:1, L4669:1, L5622:1, L5623:1, L0791:1, L0792:1, L0666:1, L2261:1, S0374:1, H0690:1, H0522:1, S0390:1, L0740:1, L0751:1, L0756:1, L0779:1 and L0731:1.
	HKFBC53	701893	239	
	HKFBC53	513190	240	
	HKFBC53	383426	241	
84	HKGDL36	877489	94	AR274:28, AR214:24, AR168:23, AR216:22, AR205:21, AR245:20, AR224:20, AR272:18, AR222:17, AR199:17, AR171:17, AR223:17, AR252:17, AR215:16, AR213:16, AR312:16, AR195:15, AR217:15, AR170:15, AR247:15, AR166:14, AR313:14, AR212:14, AR246:14, AR225:14, AR165:13, AR164:13, AR172:13, AR311:13, AR308:13, AR169:12, AR162:12, AR161:12, AR053:12, AR221:12, AR163:12, AR210:11, AR179:11, AR188:11, AR197:10, AR275:10, AR263:10, AR250:10, AR189:9, AR174:9, AR264:9, AR242:9, AR236:9, AR089:9, AR201:9, AR254:9, AR096:9, AR193:8, AR299:8, AR271:8, AR243:8, AR175:8, AR309:8, AR253:8, AR039:8, AR291:8, AR180:8, AR296:8, AR190:7, AR185:7, AR288:7, AR173:7, AR240:7, AR178:7, AR295:7, AR293:7, AR218:7, AR267:7, AR183:6, AR211:6, AR289:6, AR282:6, AR262:6, AR191:6, AR300:6, AR219:6, AR277:6, AR316:6, AR192:6, AR290:6, AR270:6, AR177:6, AR261:6, AR269:6, AR268:6, AR266:6, AR255:6, AR060:6, AR204:6, AR297:6, AR231:5, AR203:5, AR200:5, AR230:5, AR257:5, AR285:5, AR198:5, AR237:5, AR294:5, AR256:5, AR283:5, AR181:5, AR287:4, AR239:4, AR260:4, AR229:4, AR258:4, AR104:4, AR234:4, AR233:4, AR061:4, AR207:4, AR182:4, AR176:4, AR286:4, AR232:4, AR238:3, AR033:3, AR226:3, AR196:3, AR055:3, AR227:3, AR235:2, AR228:2 H0424:28, L0803:25, L0805:9, L0636:7, L0774:5, L0770:4, H0661:2, S0222:2, L0157:2, L0638:2, L3904:2, L0776:2, L0659:2, L0809:2, L0789:2, H0539:2, L0592:2, H0295:1, S0114:1, H0663:1, S6026:1, H0549:1, H0748:1, H0571:1, S0051:1, T0006:1, H0033:1, H0604:1, H0213:1, H0418:1, H0417:1, H0538:1, L0769:1, L3905:1, L0794:1, L0647:1, L0787:1,

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	HKGDL36	704088	242	
85	HKISB57	625956	95	AR161:12, AR162:12, AR163:12, AR165:12, AR164:11, AR166:11, AR089:8, AR225:7, AR178:6, AR183:6, AR172:6, AR300:5, AR224:5, AR181:5, AR221:5, AR223:5, AR170:5, AR299:5, AR039:4, AR291:4, AR096:4, AR268:4, AR275:4, AR286:4, AR274:4, AR055:4, AR247:4, AR222:4, AR269:4, AR258:4, AR257:4, AR179:3, AR240:3, AR242:3, AR173:3, AR182:3, AR262:3, AR270:3, AR272:3, AR189:3, AR316:3, AR267:3, AR175:3, AR245:3, AR313:3, AR287:3, AR296:3, AR231:2, AR210:2, AR171:2, AR190:2, AR217:2, AR205:2, AR277:2, AR230:2, AR295:2, AR290:2, AR263:2, AR060:2, AR309:2, AR191:2, AR228:2, AR229:2, AR104:2, AR261:2, AR288:2, AR174:2, AR282:2, AR246:2, AR255:2, AR312:2, AR237:2, AR169:2, AR193:2, AR271:2, AR201:2, AR233:2, AR239:2, AR197:1, AR061:1, AR226:1, AR177:1, AR213:1, AR195:1, AR033:1, AR188:1, AR238:1, AR196:1, AR185:1, AR293:1, AR176:1, AR234:1, AR227:1 L0747:5, L0731:5, H0031:4, L0599:4, S0045:3, H0411:3, H0494:3, L0783:3, L0743:3, L0758:3, L0759:3, L0604:3, H0295:2, S0356:2, S0360:2, S0046:2, H0413:2, L0774:2, H0651:2, S0027:2, L0748:2, L0439:2, L0752:2, L0601:2, H0484:1, S0132:1, H0586:1, H0333:1, H0486:1, H0042:1, H0122:1, H0546:1, H0041:1, H0050:1, H0408:1, H0288:1, H0688:1, H0424:1, H0644:1, H0383:1, L0772:1, L0764:1, L0662:1, L0364:1, L0653:1, L0782:1, L0789:1, L0666:1, L0663:1, L0664:1, H0144:1, S0148:1, H0593:1, H0666:1, S0330:1, S0044:1, S0037:1, S3014:1, L0757:1, S0031:1, H0667:1 and H0506:1.
86	HKMLM11	514788	96	AR060:13, AR039:7, AR282:7, AR170:7, AR252:7, AR263:7, AR207:7, AR309:7, AR299:6, AR224:6, AR096:5, AR161:5, AR162:5, AR264:5, AR163:5, AR311:5, AR165:5, AR214:5, AR225:5, AR235:5, AR164:5, AR277:5, AR166:5, AR308:5, AR245:5, AR246:5, AR217:5, AR182:5, AR168:4, AR283:4, AR195:4, AR275:4, AR316:4, AR271:4, AR171:4, AR312:4, AR261:4, AR053:4, AR212:4, AR222:4, AR272:4, AR270:4, AR192:4, AR213:4, AR274:4, AR193:4, AR313:4, AR173:4, AR300:4, AR286:3, AR175:3, AR089:3, AR291:3, AR180:3, AR181:3, AR269:3, AR288:3, AR223:3, AR176:3, AR169:3, AR297:3, AR289:3, AR250:3, AR285:3, AR254:3, AR201:3, AR239:3, AR229:3, AR267:3, AR104:3, AR293:3, AR198:3, AR240:3, AR230:3, AR205:3, AR243:3, AR296:3, AR196:3, AR236:3, AR227:3, AR247:3, AR216:3, AR204:3, AR172:3, AR295:3, AR268:2, AR199:2, AR257:2, AR178:2, AR055:2, AR221:2, AR237:2, AR234:2, AR174:2, AR177:2, AR287:2, AR294:2, AR188:2, AR033:2, AR238:2, AR218:2, AR231:2, AR266:2, AR210:2, AR226:2, AR228:2, AR232:2, AR185:2, AR262:2, AR061:2, AR255:2, AR233:2, AR203:2, AR191:2, AR200:2, AR260:2, AR290:2, AR189:2, AR179:2, AR258:2, AR219:2, AR197:1, AR242:1, AR183:1, AR215:1 H0620:7, L3659:3, S0442:3, H0036:3, H0150:3, S0410:2, H0722:2, H0431:2, H0012:2, L0774:2, H0740:1, H0341:1, S0358:1, H0792:1, H0549:1, H0590:1, H0746:1, H0510:1, H0059:1, T0042:1, L0475:1, L0803:1, L0775:1, H0593:1, L3215:1, S0013:1, L0758:1 and H0707:1.
87	HKMMW74	581399	97	AR229:11, AR313:11, AR163:10, AR162:10, AR161:10, AR242:9, AR176:9, AR039:9, AR204:9, AR197:8, AR309:8, AR192:8, AR180:8, AR264:8, AR181:8, AR178:8, AR089:8, AR177:8, AR164:8, AR247:7, AR268:7, AR196:7, AR239:7, AR166:7, AR182:7, AR252:7, AR271:7, AR246:7, AR282:7, AR300:7, AR165:7, AR269:7, AR233:7, AR173:7, AR174:7, AR179:7, AR267:6, AR236:6, AR228:6, AR238:6, AR175:6, AR198:6, AR096:6, AR060:6, AR299:6, AR235:6, AR257:6, AR240:6, AR261:6, AR055:6, AR293:6, AR275:6, AR226:5, AR237:5, AR185:5, AR183:5, AR243:5, AR201:5, AR234:5, AR195:5, AR250:5, AR207:5, AR291:5, AR245:5, AR316:5, AR266:5, AR191:5, AR312:5, AR053:5, AR227:5, AR231:5, AR254:5, AR230:5, AR262:5, AR270:5, AR203:5, AR224:4, AR289:4, AR263:4, AR285:4, AR212:4, AR193:4, AR199:4, AR258:4, AR216:4, AR218:4, AR061:4, AR213:4, AR255:4, AR217:4, AR297:4, AR277:4, AR200:4, AR104:4, AR272:4,

				AR232:4, AR205:4, AR274:4, AR296:4, AR295:3, AR286:3, AR033:3, AR189:3, AR287:3, AR290:3, AR256:3, AR190:3, AR311:3, AR283:3, AR169:3, AR168:3, AR170:3, AR215:3, AR253:3, AR308:3, AR288:3, AR188:3, AR171:3, AR214:3, AR223:3, AR219:2, AR294:2, AR221:2, AR260:2, AR222:2, AR172:2, AR210:1, AR225:1 H0431:1
88	HLDON23	636083	98	AR235:6, AR196:5, AR161:5, AR162:5, AR163:4, AR264:4, AR176:4, AR165:4, AR164:4, AR238:4, AR214:4, AR181:4, AR166:4, AR236:4, AR191:4, AR253:4, AR188:4, AR177:3, AR261:3, AR199:3, AR252:3, AR178:3, AR288:3, AR247:3, AR033:3, AR182:3, AR286:3, AR190:3, AR296:3, AR170:3, AR269:3, AR262:3, AR200:3, AR242:3, AR255:3, AR183:3, AR295:3, AR205:3, AR297:3, AR224:3, AR285:3, AR312:3, AR287:3, AR268:3, AR189:3, AR257:3, AR282:3, AR291:3, AR175:3, AR309:3, AR270:3, AR171:3, AR180:3, AR299:3, AR293:2, AR217:2, AR222:2, AR179:2, AR277:2, AR271:2, AR229:2, AR272:2, AR174:2, AR240:2, AR225:2, AR243:2, AR173:2, AR308:2, AR228:2, AR289:2, AR203:2, AR239:2, AR254:2, AR226:2, AR233:2, AR213:2, AR104:2, AR258:2, AR290:2, AR227:2, AR294:2, AR267:2, AR234:2, AR096:2, AR169:2, AR237:2, AR210:2, AR231:2, AR313:2, AR311:2, AR218:2, AR219:2, AR172:2, AR275:2, AR039:2, AR060:2, AR316:2, AR211:2, AR300:2, AR230:2, AR185:2, AR061:1, AR089:1, AR216:1, AR212:1, AR193:1, AR260:1, AR201:1, AR232:1, AR055:1 L0805:8, L0809:6, L0439:5, L0777:5, L0748:4, L0800:3, L0662:3, L0659:3, L0750:3, L0758:3, H0208:2, H0123:2, H0617:2, L0769:2, L0803:2, L0776:2, L0666:2, L0438:2, L0780:2, L0731:2, L3643:1, H0741:1, H0497:1, L0622:1, T0109:1, H0581:1, L0738:1, H0546:1, H0024:1, T0010:1, H0510:1, H0428:1, H0622:1, H0673:1, H0598:1, S0036:1, H0163:1, H0413:1, L0370:1, T0041:1, L0637:1, L5566:1, L0667:1, L0772:1, L0646:1, L0764:1, L0794:1, L0766:1, L0649:1, L0657:1, L0788:1, L0663:1, S0374:1, H0666:1, S0330:1, H0539:1, H0521:1, H0696:1, H0478:1, L0741:1, L0751:1, L0745:1, L0747:1, L0749:1 and L0752:1.
89	HLDQR62	753742	99	AR165:9, AR164:9, AR162:8, AR166:8, AR163:8, AR161:8, AR195:7, AR242:7, AR197:6, AR176:6, AR207:6, AR181:6, AR178:5, AR254:5, AR272:5, AR245:5, AR239:5, AR257:4, AR261:4, AR170:4, AR193:4, AR252:4, AR282:4, AR311:4, AR308:4, AR212:4, AR288:4, AR297:4, AR228:4, AR168:3, AR230:3, AR173:3, AR266:3, AR235:3, AR255:3, AR262:3, AR174:3, AR199:3, AR180:3, AR214:3, AR175:3, AR190:3, AR201:3, AR291:3, AR183:3, AR237:3, AR191:3, AR287:3, AR286:3, AR196:3, AR236:3, AR232:3, AR229:3, AR089:3, AR289:3, AR243:3, AR171:3, AR270:3, AR217:3, AR182:3, AR238:3, AR203:3, AR205:3, AR189:3, AR233:3, AR309:2, AR053:2, AR177:2, AR188:2, AR215:2, AR210:2, AR274:2, AR234:2, AR221:2, AR296:2, AR268:2, AR263:2, AR293:2, AR204:2, AR179:2, AR240:2, AR227:2, AR312:2, AR033:2, AR310:2, AR226:2, AR264:2, AR246:2, AR185:2, AR216:2, AR200:2, AR225:2, AR295:2, AR172:2, AR258:2, AR061:2, AR247:2, AR224:2, AR260:2, AR231:2, AR285:2, AR267:2, AR277:2, AR198:2, AR275:2, AR060:2, AR250:2, AR256:2, AR213:2, AR269:2, AR211:2, AR299:2, AR290:2, AR313:2, AR316:2, AR192:1, AR283:1, AR104:1, AR294:1, AR055:1, AR271:1, AR281:1, AR300:1, AR039:1, AR280:1, AR052:1 S0007:10, L0748:7, H0013:3, S0010:3, L0771:3, L0438:3, L0439:3, L0591:3, S0040:2, S0222:2, H0156:2, H0083:2, H0510:2, S0003:2, H0032:2, L3905:2, L0519:2, H0521:2, S0260:2, L0596:2, S0276:2, H0265:1, H0556:1, S0134:1, L3002:1, H0675:1, H0734:1, S0346:1, H0196:1, H0309:1, H0327:1, H0051:1, H0266:1, S0314:1, S0022:1, H0031:1, H0553:1, H0212:1, H0038:1, H0380:1, H0264:1, H0100:1, H0509:1, S0144:1, L0763:1, L0372:1, L0374:1, L0803:1, L0775:1, L0776:1, L0809:1, S0216:1, L2260:1, L0710:1, L2261:1, L2654:1, S0148:1, L3831:1, H0670:1, H0539:1, H0518:1, H0696:1, S0146:1, S0406:1, S0028:1, L0749:1, L0779:1, S0026:1, S0192:1 and S0242:1.
90	HLDQU79	740755	100	AR253:8, AR171:7, AR245:6, AR243:5, AR183:5, AR263:5, AR264:4, AR250:4, AR269:4, AR060:4, AR180:4, AR270:4, AR309:4, AR162:4, AR268:4, AR161:4, AR165:4, AR192:4, AR176:4, AR164:4, AR055:4, AR163:4, AR213:4, AR195:4,

				AR271:4, AR166:3, AR275:3, AR240:3, AR282:3, AR312:3, AR246:3, AR178:3, AR181:3, AR311:3, AR168:3, AR289:3, AR182:3, AR193:3, AR217:3, AR179:3, AR212:3, AR237:3, AR238:3, AR299:3, AR199:3, AR252:3, AR229:3, AR242:2, AR185:2, AR300:2, AR277:2, AR175:2, AR293:2, AR257:2, AR308:2, AR177:2, AR198:2, AR061:2, AR214:2, AR174:2, AR104:2, AR231:2, AR316:2, AR201:2, AR233:2, AR230:2, AR224:2, AR236:2, AR239:2, AR228:2, AR188:2, AR223:2, AR189:2, AR247:2, AR294:2, AR226:2, AR266:2, AR221:2, AR285:2, AR191:2, AR089:2, AR216:2, AR200:2, AR207:2, AR272:2, AR232:2, AR190:2, AR290:2, AR283:2, AR096:2, AR222:2, AR296:2, AR039:2, AR267:2, AR205:2, AR211:1, AR196:1, AR173:1, AR033:1, AR218:1, AR295:1, AR255:1, AR262:1, AR215:1, AR227:1, AR254:1, AR234:1, AR313:1, AR203:1, AR256:1, AR169:1, AR225:1, AR210:1, AR170:1 L0748:9, L0731:7, L0771:6, L0759:6, H0013:5, L0764:4, L0747:4, L0758:4, H0265:3, H0039:3, H0038:3, L0769:3, L0766:3, L0775:3, H0144:3, L0755:3, S0444:2, S0476:2, H0318:2, H0050:2, L0471:2, H0266:2, L0374:2, L0649:2, L0805:2, L0663:2, L0664:2, H0547:2, S0126:2, H0670:2, L0740:2, L0754:2, L0750:2, L0593:2, H0667:2, H0170:1, H0171:1, H0685:1, H0662:1, S0354:1, S0360:1, H0580:1, H0728:1, H0151:1, H0747:1, L3388:1, H0357:1, H0586:1, H0331:1, H0574:1, H0635:1, H0575:1, H0263:1, H0596:1, H0545:1, H0012:1, H0620:1, H0350:1, H0355:1, H0510:1, H0428:1, H0604:1, H0031:1, H0553:1, S0366:1, H0040:1, H0063:1, H0059:1, H0560:1, H0561:1, S0440:1, S0422:1, H0529:1, L0640:1, L0637:1, L0761:1, L0772:1, L0646:1, L4556:1, L0774:1, L0375:1, L0653:1, L0382:1, L5622:1, L0793:1, L4501:1, H0723:1, L0352:1, S0152:1, S0350:1, H0521:1, H0696:1, S0044:1, H0627:1, S0027:1, L0749:1, L0752:1, H0595:1, S0436:1, L0591:1, L0595:1, L0361:1, S0011:1, S0194:1, S0276:1 and H0423:1.
91	HLHAL68	684216	101	AR089:14, AR060:10, AR299:10, AR185:8, AR096:7, AR055:7, AR039:6, AR283:5, AR316:5, AR313:5, AR282:5, AR240:4, AR218:4, AR104:4, AR300:3, AR221:3, AR277:3, AR219:3, AR168:3, AR053:2, AR207:2, AR264:2, AR217:2, AR266:2, AR172:2, AR171:1, AR294:1, AR166:1, AR291:1, AR213:1, AR210:1, AR199:1, AR215:1, AR161:1, AR230:1, AR162:1, AR163:1 H0024:1
92	HLIBD68	778073	102	AR253:19, AR313:9, AR212:8, AR312:7, AR053:7, AR250:7, AR264:6, AR161:6, AR162:6, AR263:6, AR309:6, AR163:6, AR165:6, AR197:6, AR096:6, AR166:6, AR164:6, AR089:6, AR173:6, AR180:6, AR178:5, AR198:5, AR240:5, AR213:5, AR221:4, AR308:4, AR311:4, AR300:4, AR175:4, AR229:4, AR269:4, AR181:4, AR242:4, AR274:4, AR247:4, AR168:4, AR257:4, AR193:4, AR177:4, AR192:4, AR183:4, AR195:4, AR235:3, AR270:3, AR262:3, AR266:3, AR282:3, AR316:3, AR225:3, AR060:3, AR196:3, AR275:3, AR299:3, AR182:3, AR277:3, AR245:3, AR293:3, AR207:3, AR174:3, AR254:3, AR179:3, AR296:3, AR261:3, AR238:3, AR233:3, AR185:3, AR218:3, AR258:3, AR268:3, AR295:3, AR205:3, AR226:3, AR219:3, AR271:3, AR199:3, AR236:3, AR289:3, AR234:2, AR224:2, AR267:2, AR201:2, AR297:2, AR287:2, AR033:2, AR188:2, AR191:2, AR189:2, AR286:2, AR231:2, AR230:2, AR255:2, AR237:2, AR291:2, AR200:2, AR246:2, AR288:2, AR272:2, AR203:2, AR239:2, AR285:2, AR190:2, AR290:2, AR227:2, AR204:2, AR222:2, AR243:2, AR228:2, AR104:2, AR055:1, AR216:1, AR171:1, AR294:1, AR170:1, AR172:1, AR217:1, AR211:1 L0157:7, L0794:6, H0040:4, L0439:4, L0758:4, H0556:3, L0803:3, L0005:2, L0471:2, H0059:2, T0004:2, L0769:2, L0761:2, L0805:2, T0002:1, H0685:1, S0134:1, S0110:1, H0176:1, S0356:1, S0222:1, H0441:1, H0370:1, H0486:1, H0014:1, H0083:1, H0355:1, H0286:1, H0606:1, H0163:1, H0090:1, H0561:1, L0521:1, L0766:1, L0774:1, L0809:1, L0788:1, L0665:1, H0539:1, H0696:1, L0748:1, L0749:1, L0777:1, H0543:1 and H0423:1.
93	HLICQ90	791828	103	AR263:79, AR264:68, AR252:65, AR246:63, AR254:61, AR311:60, AR308:54, AR053:52, AR309:51, AR312:46, AR212:41, AR205:40, AR250:39, AR213:38, AR096:37, AR272:37, AR245:36, AR218:36, AR219:36, AR243:35, AR039:32, AR197:29,

				AR240:26, AR198:25, AR201:24, AR274:22, AR200:22, AR313:22, AR271:21, AR195:20, AR242:18, AR221:18, AR224:18, AR174:18, AR275:18, AR165:18, AR316:17, AR164:17, AR185:17, AR104:17, AR189:17, AR290:17, AR222:17, AR210:16, AR223:16, AR269:16, AR033:16, AR188:16, AR268:16, AR253:16, AR211:16, AR166:15, AR192:15, AR295:15, AR193:14, AR173:14, AR196:14, AR089:14, AR175:14, AR296:14, AR199:14, AR172:14, AR162:13, AR161:13, AR207:13, AR270:13, AR190:13, AR180:13, AR225:13, AR177:13, AR183:13, AR291:12, AR299:12, AR235:12, AR285:12, AR163:12, AR191:12, AR247:12, AR266:12, AR171:12, AR178:11, AR289:11, AR288:11, AR060:11, AR286:11, AR204:11, AR300:11, AR297:11, AR267:10, AR282:10, AR287:10, AR255:10, AR168:10, AR261:10, AR257:10, AR283:9, AR262:9, AR203:9, AR238:9, AR215:9, AR214:9, AR179:9, AR170:8, AR181:8, AR256:8, AR293:8, AR236:8, AR231:8, AR229:7, AR260:7, AR277:7, AR182:7, AR258:7, AR176:7, AR234:7, AR226:6, AR294:6, AR237:6, AR055:6, AR169:5, AR230:5, AR217:5, AR232:5, AR216:4, AR239:4, AR061:4, AR233:4, AR227:3, AR228:3 H0046:10, L0748:6, L0758:3, L0776:2, L0742:2, L0744:2, L0750:2, S0444:1, S0360:1, H0619:1, L0717:1, H0331:1, H0013:1, H0235:1, H0355:1, H0687:1, H0674:1, H0038:1, H0623:1, L0805:1, L0809:1, L0789:1, L0666:1, L0663:1, S0428:1, H0520:1, H0539:1, S0404:1, L0740:1, L0749:1, L0756:1, S0031:1, S0026:1 and H0008:1.
94	HLTHR66	699812	104	AR282:6, AR221:4, AR235:3, AR176:3, AR266:3, AR215:3, AR269:3, AR171:3, AR270:3, AR308:2, AR183:2, AR196:2, AR217:2, AR172:2, AR177:2, AR197:2, AR222:2, AR268:2, AR295:2, AR228:2, AR236:2, AR267:2, AR188:2, AR238:2, AR261:2, AR309:2, AR255:2, AR296:2, AR233:2, AR207:2, AR291:2, AR257:2, AR290:2, AR232:2, AR193:1, AR277:1, AR178:1, AR283:1, AR089:1, AR181:1, AR164:1, AR203:1, AR264:1, AR212:1, AR166:1, AR231:1, AR247:1, AR293:1, AR205:1, AR055:1, AR316:1, AR300:1, AR175:1, AR287:1, AR189:1, AR168:1, AR234:1, AR161:1, AR174:1, AR239:1 H0036:2, S0132:1, S0010:1, S0250:1, H0591:1 and H0130:1.
95	HLTIP94	1087335	105	AR060:7, AR055:7, AR185:6, AR313:6, AR218:5, AR300:5, AR240:5, AR089:4, AR282:4, AR299:4, AR283:4, AR039:3, AR096:3, AR316:3, AR104:3, AR277:3, AR219:2 H0170:1, S6026:1 and H0591:1.
	HLTIP94	1035443	243	
	HLTIP94	1047690	244	
96	HLWAA17	629552	106	AR273:12, AR184:12, AR248:11, AR281:9, AR183:8, AR265:8, AR314:7, AR280:7, AR315:7, AR269:7, AR268:6, AR270:6, AR241:6, AR290:6, AR249:5, AR298:5, AR244:5, AR292:5, AR274:4, AR096:4, AR291:4, AR271:4, AR238:4, AR251:4, AR310:4, AR052:4, AR309:4, AR215:4, AR198:4, AR182:4, AR219:4, AR226:4, AR312:4, AR206:4, AR275:4, AR243:4, AR313:4, AR267:4, AR231:4, AR186:4, AR218:4, AR272:4, AR282:4, AR253:4, AR165:4, AR225:4, AR164:3, AR192:3, AR296:3, AR240:3, AR242:3, AR039:3, AR311:3, AR284:3, AR232:3, AR089:3, AR175:3, AR237:3, AR196:3, AR207:3, AR213:3, AR161:3, AR061:3, AR234:3, AR285:3, AR247:3, AR227:3, AR185:3, AR216:3, AR229:3, AR289:2, AR053:2, AR033:2, AR277:2, AR193:2, AR195:2, AR205:2, AR316:2, AR264:2, AR212:2, AR286:2, AR188:2, AR293:2, AR174:2, AR297:2, AR222:2, AR300:2, AR191:2, AR190:2, AR177:2, AR288:2, AR295:2, AR283:2, AR162:2, AR263:2, AR055:2, AR299:2, AR104:2, AR261:2, AR166:2, AR294:2, AR266:2, AR181:2, AR214:2, AR189:2, AR259:2, AR246:2, AR201:1, AR060:1, AR257:1, AR204:1, AR233:1, AR199:1, AR179:1, AR173:1, AR200:1, AR258:1, AR210:1, AR252:1, AR168:1, AR256:1, AR194:1, AR255:1, AR236:1 S0410:24, L0748:18, S0436:12, H0547:8, L0731:8, H0556:7, H0039:6, L0666:6, H0046:5, H0059:5, L0775:5, L0439:5, L0755:5, H0622:4, L0662:4, L0740:4, L0751:4, L0779:4, H0575:3, H0553:3, H0529:3, L0769:3, L0659:3, L5623:3, L0588:3, L0593:3, S0011:3, H0255:2, S0418:2, S0442:2, S0046:2, H0586:2, S0049:2,

				H0424:2, H0644:2, H0560:2, H0561:2, S0002:2, S0426:2, L0763:2, L0772:2, L0646:2, L0655:2, L0527:2, L0518:2, L0783:2, L0809:2, L0665:2, L0438:2, H0519:2, H0689:2, H0672:2, H0555:2, H0631:2, S0206:2, L0757:2, L0758:2, L0485:2, L0608:2, L0601:2, H0543:2, H0171:1, H0265:1, S0040:1, H0294:1, T0049:1, S0134:1, H0583:1, H0657:1, H0484:1, H0661:1, H0125:1, S0420:1, S0354:1, S0358:1, S0360:1, S0408:1, H0580:1, H0742:1, S0132:1, S0476:1, H0550:1, H0431:1, H0592:1, H0587:1, H0333:1, H0270:1, H0013:1, H0599:1, T0082:1, H0318:1, H0251:1, T0110:1, H0545:1, H0150:1, H0041:1, H0620:1, H0024:1, H0057:1, H0014:1, S0051:1, H0083:1, S0024:1, H0355:1, H0266:1, H0271:1, H0188:1, S0250:1, H0328:1, H0615:1, L0483:1, H0030:1, H0031:1, H0111:1, H0032:1, H0383:1, H0674:1, H0211:1, L0456:1, H0068:1, H0135:1, H0040:1, H0634:1, H0551:1, H0412:1, S0450:1, H0647:1, H0646:1, S0144:1, S0142:1, S0344:1, S0210:1, L0761:1, L0372:1, L0764:1, L0767:1, L0768:1, L0649:1, L5574:1, L0375:1, L0651:1, L0784:1, L0654:1, L0807:1, L0515:1, L0658:1, L0383:1, L0663:1, L0664:1, S0006:1, H0520:1, H0593:1, H0682:1, H0684:1, H0658:1, H0670:1, H0696:1, S0406:1, S0027:1, L0754:1, L0747:1, L0750:1, L0752:1, S0434:1, L0591:1, L0603:1, S0106:1, H0668:1, H0542:1 and H0423:1.
97	HLYAC95	778075	107	AR176:19, AR182:14, AR261:10, AR192:9, AR262:9, AR191:8, AR255:7, AR296:7, AR231:7, AR201:6, AR232:6, AR234:6, AR233:6, AR228:6, AR183:6, AR246:6, AR229:6, AR239:6, AR200:6, AR287:5, AR207:5, AR291:5, AR260:5, AR294:5, AR245:5, AR179:5, AR243:5, AR266:5, AR177:5, AR168:5, AR285:5, AR162:5, AR289:5, AR185:4, AR237:4, AR161:4, AR221:4, AR236:4, AR264:4, AR274:4, AR227:4, AR215:4, AR222:4, AR223:4, AR309:4, AR193:4, AR290:4, AR313:3, AR196:3, AR263:3, AR174:3, AR204:3, AR293:3, AR205:3, AR189:3, AR217:3, AR282:3, AR033:3, AR257:3, AR288:3, AR203:3, AR312:2, AR267:2, AR275:2, AR277:2, AR216:2, AR295:2, AR311:2, AR258:2, AR316:2, AR181:2, AR225:2, AR061:2, AR214:2, AR240:2, AR039:2, AR299:2, AR170:2, AR252:2, AR199:2, AR238:2, AR247:2, AR256:2, AR089:2, AR224:2, AR219:2, AR096:2, AR211:2, AR060:1, AR188:1, AR175:1, AR300:1, AR226:1, AR173:1, AR286:1, AR269:1 H0445:1
98	HMADK33	561941	108	AR283:32, AR096:20, AR089:18, AR218:17, AR104:17, AR277:16, AR039:16, AR316:15, AR282:15, AR055:13, AR219:13, AR060:13, AR313:13, AR299:12, AR252:9, AR185:8, AR240:8, AR300:8, AR253:8, AR271:7, AR245:6, AR309:6, AR215:6, AR170:6, AR198:6, AR195:5, AR169:5, AR053:5, AR254:5, AR311:5, AR214:5, AR264:5, AR225:5, AR223:5, AR224:5, AR197:5, AR263:5, AR266:4, AR217:4, AR312:4, AR193:4, AR308:4, AR161:4, AR213:4, AR162:4, AR180:4, AR212:4, AR163:4, AR216:4, AR168:4, AR291:4, AR222:4, AR295:4, AR177:4, AR183:4, AR165:4, AR275:4, AR192:4, AR221:4, AR235:4, AR261:4, AR269:3, AR270:3, AR176:3, AR164:3, AR210:3, AR288:3, AR172:3, AR033:3, AR205:3, AR181:3, AR246:3, AR166:3, AR171:3, AR175:3, AR236:3, AR296:3, AR285:3, AR188:3, AR207:3, AR247:3, AR199:3, AR201:3, AR243:3, AR267:3, AR297:3, AR293:3, AR255:3, AR182:3, AR294:3, AR268:2, AR286:2, AR289:2, AR257:2, AR204:2, AR287:2, AR258:2, AR230:2, AR200:2, AR173:2, AR196:2, AR238:2, AR274:2, AR174:2, AR262:2, AR189:2, AR228:2, AR179:2, AR211:2, AR191:2, AR231:2, AR290:2, AR203:2, AR232:2, AR229:2, AR233:2, AR190:2, AR227:2, AR272:2, AR234:2, AR239:2, AR178:2, AR237:2, AR061:1, AR226:1, AR260:1, AR256:1 L0438:9, L0439:9, L0776:8, H0144:7, L0741:7, H0271:6, S0222:5, L0769:5, H0052:4, L0770:4, L0766:4, L0659:4, L0666:4, L0759:4, H0295:3, S0360:3, L0370:3, L0510:3, H0556:2, S0007:2, H0261:2, L0021:2, H0046:2, H0009:2, S0051:2, S0366:2, H0059:2, L0763:2, L0784:2, L0633:2, L0783:2, L0789:2, L0790:2, L0792:2, L0743:2, L0747:2, L0749:2, L0756:2, L0757:2, L0758:2, H0445:2, L0588:2, L0594:2, L0366:2, H0265:1, S6024:1, H0638:1, S0376:1, S0045:1, H0550:1, H0370:1, H0587:1, N0009:1, H0013:1, S0280:1, H0599:1, S0010:1, S0049:1, H0545:1, H0457:1, H0569:1, H0012:1, H0373:1, H0051:1, H0510:1, H0266:1, H0179:1,

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99	HMAMI15	1352406	109	AR060:14, AR283:13, AR055:10, AR277:9, AR282:9, AR185:9, AR104:9, AR300:8, AR096:8, AR316:8, AR299:8, AR218:7, AR219:7, AR039:7, AR313:6, AR240:6, AR089:6 H0624:2, S0354:2, S0442:1, S0444:1, S0278:1, S0222:1, H0586:1, L0021:1, H0036:1, H0031:1, L0769:1, L0804:1, L0774:1, H0658:1, H0521:1, S0406:1, L0748:1 and S0462:1.
	HMAMI15	1049263	245	
100	HMCFY13	635301	110	AR176:8, AR161:6, AR162:6, AR266:6, AR181:6, AR269:6, AR163:6, AR172:6, AR228:5, AR267:5, AR233:5, AR055:5, AR268:5, AR229:5, AR165:5, AR309:5, AR238:4, AR183:4, AR178:4, AR164:4, AR237:4, AR215:4, AR257:4, AR182:4, AR166:4, AR168:4, AR217:4, AR236:4, AR239:4,.AR261:4, AR180:4, AR291:4, AR222:4, AR290:4, AR270:4, AR170:4, AR177:4, AR060:4, AR240:4, AR282:4, AR247:4, AR272:4, AR275:4, AR293:4, AR288:4, AR171:3, AR169:3, AR255:3, AR289:3, AR179:3, AR203:3, AR175:3, AR264:3, AR231:3, AR061:3, AR225:3, AR191:3, AR294:3, AR287:3, AR230:3, AR223:3, AR226:3, AR173:3, AR232:3, AR234:3, AR200:3, AR214:3, AR216:3, AR221:3, AR224:3, AR196:3, AR227:3, AR104:3, AR199:3, AR285:3, AR262:3, AR277:2, AR311:2, AR297:2, AR300:2, AR096:2, AR190:2, AR295:2, AR174:2, AR188:2, AR316:2, AR286:2, AR312:2, AR089:2, AR263:2, AR189:2, AR313:2, AR258:2, AR274:2, AR053:2, AR283:2, AR299:2, AR185:1, AR296:1, AR204:1, AR260:1, AR210:1, AR039:1, AR218:1 L0800:2, H0550:1, H0497:1, S0344:1, L0769:1, L0789:1 and L0749:1.
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102	HMEED18	560775	112	AR252:37, AR186:32, AR250:28, AR169:20, AR254:19, AR207:17, AR244:17, AR195:16, AR033:15, AR284:15, AR291:15, AR214:14, AR165:14, AR298:14, AR264:14, AR222:14, AR181:13, AR245:13, AR164:13, AR197:13, AR246:13, AR224:13, AR168:13, AR253:13, AR308:13, AR223:12, AR269:12, AR285:12, AR225:12, AR263:12, AR212:12, AR172:12, AR166:12, AR274:12, AR311:12, AR162:12, AR161:12, AR163:12, AR184:12, AR215:11, AR192:11, AR221:11, AR052:11, AR240:11, AR104:11, AR183:11, AR171:11, AR174:11, AR170:11, AR176:11, AR173:11, AR193:11, AR206:11, AR201:11, AR053:11, AR292:10, AR288:10, AR231:10, AR237:10, AR261:10, AR235:10, AR295:10, AR273:10, AR236:10, AR293:10, AR312:10, AR216:10, AR205:10, AR217:10, AR178:10, AR196:10, AR213:10, AR061:10, AR270:9, AR243:9, AR290:9, AR282:9, AR191:9, AR182:9, AR268:9, AR188:9, AR286:9, AR267:9, AR189:9, AR238:9, AR229:9, AR177:9, AR226:9, AR294:9, AR242:9, AR289:9, AR175:8, AR299:8, AR310:8, AR266:8, AR199:8, AR096:8, AR247:8, AR039:8, AR297:8, AR180:8, AR227:8, AR296:8, AR271:8, AR190:8, AR313:8, AR309:8, AR194:7, AR287:7, AR234:7, AR185:7, AR275:7, AR248:7, AR210:7, AR200:7, AR089:7, AR277:7, AR300:7, AR316:7, AR204:7, AR272:7, AR179:7, AR251:6, AR259:6, AR262:6, AR211:6, AR255:6, AR241:6, AR314:6, AR055:6, AR198:6, AR256:6, AR257:6, AR258:6, AR232:6, AR203:5, AR239:5,

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103	HMEFT54	520307	113	AR060:7, AR055:7, AR039:6, AR282:6, AR223:5, AR196:5, AR089:5, AR104:5, AR269:5, AR176:5, AR161:5, AR162:5, AR182:5, AR240:5, AR163:5, AR096:5, AR231:5, AR165:5, AR299:5, AR235:5, AR207:5, AR309:5, AR204:5, AR313:4, AR243:4, AR181:4, AR246:4, AR316:4, AR164:4, AR166:4, AR300:4, AR277:4, AR183:4, AR170:4, AR228:4, AR185:4, AR229:4, AR255:4, AR274:4, AR221:4, AR266:4, AR283:4, AR247:4, AR290:4, AR236:4, AR261:4, AR294:4, AR267:3, AR192:3, AR270:3, AR178:3, AR175:3, AR169:3, AR234:3, AR179:3, AR275:3, AR262:3, AR252:3, AR199:3, AR197:3, AR219:3, AR253:3, AR233:3, AR061:3, AR264:3, AR271:3, AR180:3, AR173:3, AR263:3, AR295:3, AR193:3, AR177:3, AR288:3, AR237:3, AR257:3, AR268:3, AR195:3, AR174:3, AR286:3, AR218:3, AR191:3, AR239:3, AR171:3, AR203:3, AR250:3, AR285:3, AR287:3, AR188:3, AR216:3, AR297:3, AR296:3, AR189:3, AR201:3, AR214:2, AR226:2, AR291:2, AR293:2, AR232:2, AR222:2, AR200:2, AR190:2, AR258:2, AR168:2, AR227:2, AR312:2, AR289:2, AR308:2, AR260:2, AR230:2, AR272:1, AR210:1, AR311:1, AR242:1, AR256:1, AR033:1 L0757:3, L0662:2, H0686:1, S0444:1, H0266:1, L0055:1, L0763:1, L0800:1, L0764:1, L0768:1, L0805:1, L0653:1, L0666:1, H0690:1, H0672:1, L0751:1, L0777:1 and L0758:1.
104	HMEGF92	520304	114	AR233:16, AR178:13, AR176:13, AR261:11, AR061:11, AR257:11, AR104:11, AR228:10, AR182:10, AR196:10, AR238:10, AR299:9, AR236:9, AR293:8, AR239:8, AR190:8, AR231:8, AR288:8, AR232:8, AR291:8, AR161:8, AR229:8, AR162:8, AR175:8, AR163:7, AR258:7, AR269:7, AR185:7, AR266:7, AR033:7, AR174:7, AR164:6, AR200:6, AR191:6, AR300:6, AR250:6, AR237:6, AR234:6, AR267:6, AR287:6, AR166:6, AR165:5, AR294:5, AR203:5, AR286:5, AR268:5, AR262:5, AR055:5, AR247:5, AR226:5, AR285:5, AR179:5, AR295:5, AR089:5, AR230:5, AR216:5, AR316:5, AR183:5, AR252:5, AR297:5, AR181:5, AR060:5, AR271:5, AR168:4, AR172:4, AR193:4, AR240:4, AR264:4, AR227:4, AR180:4, AR207:4, AR309:4, AR188:4, AR296:4, AR177:4, AR275:4, AR289:4, AR189:4, AR255:3, AR198:3, AR235:3, AR215:3, AR260:3, AR171:3, AR246:3, AR096:3, AR313:3, AR290:3, AR214:3, AR221:3, AR274:2, AR039:2, AR217:2, AR197:2, AR210:2, AR204:2, AR312:2, AR213:2, AR277:2, AR272:2, AR225:2, AR199:2, AR222:2, AR211:2, AR053:2, AR308:2, AR311:2, AR224:2, AR173:1, AR270:1, AR282:1, AR283:1, AR201:1 H0266:1, L0438:1 and L0439:1.
105	HMSDL37	973996	115	AR169:5, AR282:3, AR170:3, AR225:2, AR257:2, AR224:2, AR205:2, AR171:2, AR294:2, AR217:1, AR309:1, AR168:1, AR261:1, AR173:1, AR163:1, AR222:1, AR178:1 L0517:2, S0050:1, H0014:1, H0510:1, H0040:1, H0264:1, S0002:1, S0374:1 and L0758:1.
	HMSDL37	895429	246	
	HMSDL37	904241	247	
	HMSDL37	750927	248	

106	HMSFI26	560229	116	AR313:11, AR039:11, AR089:8, AR096:8, AR218:8, AR176:7, AR162:7, AR219:7, AR163:7, AR161:7, AR299:6, AR165:6, AR300:6, AR221:6, AR180:6, AR060:6, AR164:6, AR166:6, AR207:6, AR197:6, AR178:6, AR182:6, AR175:6, AR316:6, AR181:6, AR173:6, AR055:6, AR104:5, AR266:5, AR247:5, AR270:5, AR204:5, AR229:5, AR185:5, AR240:5, AR183:5, AR312:5, AR177:5, AR309:5, AR196:4, AR257:4, AR297:4, AR263:4, AR243:4, AR277:4, AR193:4, AR293:4, AR225:4, AR269:4, AR264:4, AR179:4, AR275:4, AR282:4, AR226:4, AR261:4, AR205:4, AR242:4, AR268:4, AR294:4, AR291:4, AR233:4, AR267:4, AR262:4, AR296:4, AR238:3, AR234:3, AR228:3, AR289:3, AR174:3, AR199:3, AR237:3, AR231:3, AR271:3, AR195:3, AR258:3, AR236:3, AR245:3, AR198:3, AR215:3, AR283:3, AR227:3, AR239:3, AR212:3, AR203:3, AR170:3, AR246:3, AR286:3, AR290:3, AR285:3, AR230:3, AR295:3, AR053:3, AR201:3, AR191:3, AR255:2, AR308:2, AR272:2, AR168:2, AR033:2, AR287:2, AR217:2, AR188:2, AR222:2, AR200:2, AR061:2, AR232:2, AR189:2, AR216:2, AR288:2, AR213:2, AR274:2, AR311:2, AR171:2, AR260:2, AR190:2, AR224:2, AR210:1, AR169:1 S0002:1
107	HMVBS81	639203	117	AR215:22, AR223:21, AR214:21, AR172:20, AR225:18, AR210:16, AR170:15, AR291:14, AR199:14, AR169:14, AR224:14, AR216:14, AR171:14, AR222:13, AR168:13, AR211:12, AR221:11, AR165:11, AR231:11, AR164:11, AR166:11, AR219:11, AR289:10, AR217:10, AR061:10, AR266:10, AR235:10, AR285:10, AR283:9, AR196:9, AR218:9, AR162:9, AR243:9, AR161:9, AR261:9, AR089:9, AR163:9, AR238:8, AR255:8, AR240:8, AR200:8, AR297:8, AR296:8, AR254:8, AR287:8, AR269:8, AR245:8, AR295:7, AR290:7, AR039:7, AR246:7, AR316:7, AR282:7, AR257:7, AR247:7, AR189:7, AR226:7, AR173:7, AR188:7, AR239:7, AR183:7, AR232:7, AR180:7, AR178:7, AR256:7, AR203:6, AR250:6, AR288:6, AR267:6, AR193:6, AR234:6, AR268:6, AR237:6, AR182:6, AR176:6, AR229:6, AR293:6, AR262:6, AR175:6, AR270:5, AR212:5, AR177:5, AR205:5, AR258:5, AR272:5, AR198:5, AR236:5, AR191:5, AR185:5, AR104:5, AR312:5, AR311:5, AR174:5, AR300:5, AR060:5, AR286:5, AR195:5, AR260:5, AR233:4, AR294:4, AR263:4, AR190:4, AR308:4, AR228:4, AR230:4, AR299:4, AR179:4, AR277:4, AR227:4, AR271:4, AR096:4, AR213:4, AR275:4, AR055:4, AR264:4, AR313:4, AR201:4, AR053:4, AR197:3, AR033:3, AR181:3, AR242:3, AR253:3, AR274:3, AR207:2, AR204:2, AR309:2, AR252:2, AR192:1 H0544:4, L0775:3, L0748:3, H0265:2, H0046:2, T0010:2, H0424:2, L0769:2, L0771:2, L0774:2, L0659:2, L0382:2, H0696:2, L0750:2, L0755:2, L0731:2, L0757:2, L0758:2, L0608:2, H0685:1, S0040:1, S0114:1, S0218:1, L0785:1, H0341:1, S0212:1, H0484:1, H0662:1, S0360:1, H0411:1, H0592:1, L0623:1, H0156:1, H0253:1, H0263:1, H0204:1, H0150:1, H0050:1, H0012:1, H0510:1, H0606:1, L0055:1, S0364:1, H0124:1, H0163:1, H0090:1, H0087:1, H0413:1, H0494:1, H0509:1, S0210:1, L0770:1, L0764:1, L0773:1, L0794:1, L0766:1, L0658:1, L0666:1, S0126:1, S3012:1, S3014:1, L0745:1, L0747:1, L0777:1, S0031:1, S0434:1, L0605:1, L0366:1 and H0543:1.
108	HMWDC28	460487	118	AR245:5, AR176:5, AR198:5, AR161:5, AR162:4, AR204:4, AR163:4, AR207:4, AR271:4, AR309:4, AR266:4, AR164:4, AR165:4, AR166:4, AR181:3, AR221:3, AR039:3, AR252:3, AR089:3, AR254:3, AR216:3, AR182:3, AR291:3, AR177:3, AR257:3, AR224:3, AR264:3, AR312:3, AR268:3, AR238:3, AR275:3, AR296:3, AR178:2, AR179:2, AR228:2, AR215:2, AR267:2, AR196:2, AR229:2, AR295:2, AR311:2, AR055:2, AR233:2, AR282:2, AR096:2, AR270:2, AR288:2, AR269:2, AR191:2, AR246:2, AR289:2, AR053:2, AR185:2, AR300:2, AR285:2, AR286:2, AR234:2, AR236:2, AR262:2, AR316:2, AR174:2, AR255:2, AR231:2, AR313:2, AR060:2, AR201:2, AR294:2, AR287:2, AR237:2, AR243:2, AR212:2, AR240:2, AR226:2, AR232:2, AR290:2, AR283:2, AR061:2, AR261:2, AR308:2, AR168:2, AR247:2, AR203:2, AR239:2, AR253:2, AR175:2, AR277:2, AR217:2, AR293:1, AR190:1, AR272:1, AR193:1, AR227:1, AR297:1, AR213:1, AR230:1, AR258:1, AR188:1, AR180:1, AR033:1, AR195:1, AR199:1, AR183:1, AR211:1, AR235:1 H0341:2, L0803:2, L0439:2, L0747:2,

				S0376:1, S0360:1, S0222:1, H0674:1, H0038:1, L0655:1, L0809:1, L0666:1, L0754:1, L0756:1, L0757:1 and L0591:1.
109	HMWFT65	562063	119	AR176:6, AR183:6, AR313:6, AR173:6, AR269:6, AR290:6, AR180:6, AR247:5, AR189:5, AR162:5, AR191:5, AR161:5, AR163:5, AR039:5, AR266:5, AR274:4, AR182:4, AR055:4, AR060:4, AR165:4, AR190:4, AR263:4, AR164:4, AR270:4, AR166:4, AR264:4, AR089:4, AR267:4, AR096:4, AR175:4, AR181:4, AR168:3, AR255:3, AR170:3, AR257:3, AR169:3, AR179:3, AR293:3, AR196:3, AR178:3, AR217:3, AR268:3, AR275:3, AR262:3, AR291:3, AR233:3, AR229:3, AR240:3, AR237:3, AR238:3, AR218:3, AR185:3, AR228:3, AR294:3, AR171:3, AR250:3, AR316:3, AR300:3, AR188:3, AR104:3, AR174:3, AR231:3, AR296:3, AR225:3, AR224:3, AR177:3, AR261:3, AR236:3, AR061:3, AR239:3, AR226:3, AR299:3, AR285:3, AR288:3, AR277:2, AR198:2, AR272:2, AR193:2, AR201:2, AR221:2, AR200:2, AR287:2, AR230:2, AR203:2, AR286:2, AR232:2, AR289:2, AR227:2, AR214:2, AR199:2, AR295:2, AR172:2, AR297:2, AR033:2, AR282:2, AR308:2, AR219:2, AR223:2, AR258:2, AR283:2, AR271:2, AR311:1, AR260:1, AR216:1, AR234:1, AR312:1, AR245:1, AR211:1, AR212:1, AR235:1, AR195:1 H0341:1
110	HNEEE24	553558	120	AR161:8, AR162:8, AR163:8, AR055:6, AR165:5, AR166:5, AR164:5, AR060:5, AR172:5, AR313:4, AR169:4, AR053:4, AR269:4, AR275:4, AR089:4, AR242:4, AR263:4, AR176:4, AR264:4, AR192:4, AR240:3, AR182:3, AR205:3, AR039:3, AR235:3, AR096:3, AR212:3, AR257:3, AR268:3, AR282:3, AR195:3, AR270:3, AR104:3, AR200:3, AR197:3, AR228:3, AR185:3, AR173:3, AR316:3, AR299:3, AR233:3, AR236:3, AR189:3, AR191:3, AR283:3, AR311:3, AR300:2, AR309:2, AR267:2, AR255:2, AR229:2, AR225:2, AR245:2, AR290:2, AR295:2, AR193:2, AR308:2, AR312:2, AR277:2, AR266:2, AR237:2, AR221:2, AR199:2, AR274:2, AR238:2, AR224:2, AR262:2, AR213:2, AR181:2, AR216:2, AR180:2, AR218:2, AR261:2, AR061:2, AR247:2, AR289:2, AR178:2, AR287:2, AR175:2, AR293:2, AR297:2, AR177:2, AR190:2, AR285:2, AR226:2, AR231:2, AR219:2, AR183:2, AR179:2, AR239:2, AR196:2, AR291:2, AR217:2, AR201:2, AR288:2, AR227:1, AR272:1, AR258:1, AR294:1, AR296:1, AR232:1, AR214:1, AR260:1, AR168:1, AR174:1, AR171:1 L0747:2, L0758:2, H0580:1 and H0179:1.
111	HNFFC43	753337	121	AR273:25, AR052:20, AR274:13, AR218:10, AR241:9, AR248:9, AR277:8, AR265:8, AR186:8, AR249:8, AR312:8, AR271:8, AR313:8, AR309:7, AR183:7, AR253:7, AR299:7, AR244:6, AR251:6, AR292:6, AR219:6, AR175:6, AR310:6, AR096:5, AR213:5, AR185:5, AR053:5, AR275:5, AR202:5, AR282:5, AR039:4, AR269:4, AR270:4, AR206:4, AR055:4, AR177:4, AR225:4, AR089:4, AR060:4, AR192:4, AR293:4, AR243:4, AR280:4, AR247:4, AR300:4, AR104:4, AR033:4, AR240:4, AR061:3, AR204:3, AR217:3, AR246:3, AR316:3, AR268:3, AR165:3, AR180:3, AR198:3, AR315:3, AR164:3, AR166:3, AR184:3, AR205:3, AR264:3, AR294:3, AR314:3, AR284:3, AR290:3, AR295:2, AR168:2, AR259:2, AR267:2, AR256:2, AR179:2, AR161:2, AR221:2, AR257:2, AR163:2, AR162:2, AR170:2, AR291:2, AR200:2, AR236:2, AR262:2, AR193:2, AR283:2, AR174:2, AR197:2, AR298:2, AR233:1, AR181:1, AR222:1, AR287:1, AR258:1, AR195:1, AR194:1, AR229:1, AR196:1, AR182:1, AR173:1, AR234:1, AR239:1, AR235:1, AR230:1, AR216:1 H0521:6, H0036:2, H0052:2, H0271:2, H0551:2, H0543:2, H0265:1, H0556:1, S0354:1, H0392:1, H0581:1, H0063:1, H0059:1, H0494:1, H0561:1, L3829:1, H0520:1, H0522:1, S0436:1, L0595:1, H0506:1 and L0600:1.
112	HNFIY77	634551	122	AR241:9, AR313:8, AR194:8, AR186:7, AR192:7, AR242:7, AR202:7, AR206:7, AR161:7, AR162:7, AR163:6, AR204:6, AR246:6, AR229:6, AR165:6, AR238:6, AR164:6, AR166:5, AR271:5, AR198:5, AR251:5, AR089:5, AR207:5, AR197:5, AR052:5, AR309:5, AR312:5, AR274:5, AR243:5, AR061:4, AR185:4, AR292:4, AR177:4, AR298:4, AR245:4, AR226:4, AR273:4, AR240:4, AR053:4, AR225:4, AR286:4, AR233:4, AR272:4, AR300:4, AR096:4, AR293:4, AR247:4, AR264:4,

				AR205:4, AR039:4, AR234:4, AR275:3, AR237:3, AR231:3, AR195:3, AR253:3, AR060:3, AR228:3, AR201:3, AR182:3, AR284:3, AR282:3, AR174:3, AR227:3, AR269:3, AR193:3, AR199:3, AR289:3, AR033:3, AR294:3, AR239:3, AR285:3, AR290:3, AR184:3, AR270:3, AR265:3, AR308:3, AR181:3, AR248:3, AR232:3, AR296:3, AR291:3, AR299:3, AR297:3, AR252:3, AR259:3, AR277:3, AR310:2, AR263:2, AR230:2, AR258:2, AR288:2, AR224:2, AR257:2, AR295:2, AR203:2, AR213:2, AR179:2, AR055:2, AR268:2, AR104:2, AR200:2, AR316:2, AR255:2, AR212:2, AR267:2, AR215:2, AR266:2, AR183:2, AR173:2, AR175:2, AR191:2, AR287:2, AR217:2, AR222:2, AR172:2, AR196:2, AR281:1, AR189:1, AR283:1, AR218:1, AR219:1, AR214:1, AR256:1, AR262:1, AR216:1, AR210:1 L0539:1, S0442:1, H0619:1, H0581:1, T0010:1, H0416:1, H0622:1, H0131:1, H0521:1 and H0653:1.
113	HNFJF07	577013	123	AR104:20, AR055:15, AR060:14, AR229:13, AR283:12, AR039:11, AR313:10, AR089:10, AR096:9, AR316:9, AR161:8, AR162:8, AR299:8, AR163:8, AR165:7, AR282:7, AR164:7, AR166:7, AR185:6, AR240:6, AR300:6, AR274:6, AR219:5, AR053:5, AR277:5, AR263:5, AR309:5, AR275:5, AR172:5, AR181:4, AR250:4, AR257:4, AR236:4, AR177:4, AR218:4, AR261:4, AR228:4, AR171:4, AR266:4, AR183:4, AR178:4, AR238:4, AR264:4, AR225:4, AR235:4, AR255:3, AR215:3, AR293:3, AR286:3, AR233:3, AR179:3, AR222:3, AR234:3, AR262:3, AR237:3, AR247:3, AR182:3, AR287:3, AR168:3, AR272:3, AR294:3, AR288:3, AR170:3, AR196:3, AR174:3, AR269:3, AR175:3, AR297:3, AR268:3, AR226:3, AR223:3, AR201:3, AR311:3, AR239:3, AR290:3, AR200:3, AR231:3, AR308:2, AR195:2, AR199:2, AR061:2, AR227:2, AR216:2, AR285:2, AR312:2, AR296:2, AR271:2, AR232:2, AR180:2, AR270:2, AR291:2, AR258:2, AR230:2, AR191:2, AR289:2, AR224:1, AR246:1, AR295:1, AR188:1, AR193:1, AR217:1, AR242:1, AR214:1 H0271:2, H0581:1, H0051:1, H0163:1, L0599:1 and H0422:1.
114	HNGFR31	553552	124	AR060:6, AR252:6, AR055:6, AR053:5, AR161:4, AR162:4, AR254:4, AR163:4, AR309:4, AR089:4, AR235:3, AR236:3, AR104:3, AR283:3, AR165:3, AR216:3, AR164:3, AR300:3, AR166:3, AR181:3, AR185:3, AR177:3, AR228:3, AR263:3, AR299:3, AR183:3, AR267:3, AR039:3, AR182:3, AR176:2, AR197:2, AR240:2, AR201:2, AR277:2, AR289:2, AR291:2, AR282:2, AR266:2, AR293:2, AR316:2, AR255:2, AR096:2, AR238:2, AR180:2, AR257:2, AR175:2, AR218:2, AR233:2, AR215:2, AR285:2, AR264:2, AR231:2, AR239:2, AR274:2, AR229:2, AR207:2, AR262:2, AR179:2, AR286:2, AR173:2, AR288:2, AR188:2, AR198:2, AR214:2, AR192:2, AR287:2, AR190:2, AR261:2, AR237:2, AR211:2, AR297:2, AR313:2, AR178:2, AR200:2, AR247:2, AR227:2, AR270:2, AR203:2, AR269:2, AR226:2, AR290:2, AR191:2, AR212:1, AR219:1, AR268:1, AR271:1, AR275:1, AR272:1, AR189:1, AR168:1, AR294:1, AR312:1, AR174:1, AR224:1, AR234:1, AR061:1, AR193:1, AR213:1, AR258:1, AR311:1, AR222:1 S0052:1
115	HNGIJ31	519120	125	AR231:7, AR039:6, AR221:5, AR313:4, AR096:4, AR180:4, AR055:4, AR060:4, AR104:4, AR161:4, AR162:4, AR163:4, AR275:4, AR183:4, AR089:3, AR205:3, AR300:3, AR272:3, AR246:3, AR274:3, AR225:3, AR269:3, AR181:3, AR299:3, AR165:3, AR164:3, AR166:3, AR175:3, AR173:3, AR191:3, AR198:3, AR277:3, AR185:3, AR270:3, AR182:3, AR240:3, AR033:3, AR316:3, AR176:2, AR267:2, AR261:2, AR204:2, AR266:2, AR257:2, AR291:2, AR216:2, AR218:2, AR264:2, AR214:2, AR219:2, AR222:2, AR224:2, AR195:2, AR189:2, AR190:2, AR201:2, AR283:2, AR288:2, AR196:2, AR309:2, AR179:2, AR285:2, AR271:2, AR290:2, AR263:2, AR296:2, AR282:2, AR172:2, AR178:2, AR293:2, AR193:2, AR226:2, AR233:1, AR199:1, AR312:1, AR234:1, AR228:1, AR247:1, AR230:1, AR061:1, AR255:1, AR188:1, AR238:1, AR287:1, AR268:1, AR236:1, AR217:1, AR258:1, AR262:1, AR174:1, AR295:1, AR192:1
116	HNGJE50	561568	126	AR039:15, AR313:14, AR161:14, AR162:14, AR163:13, AR165:12, AR166:11, AR164:11, AR089:11, AR096:10, AR178:9,

				AR229:9, AR299:8, AR300:8, AR198:8, AR060:7, AR185:7, AR245:7, AR271:7, AR182:7, AR176:7, AR053:7, AR180:7, AR316:7, AR247:7, AR240:6, AR173:6, AR274:6, AR055:6, AR266:6, AR181:6, AR257:6, AR175:6, AR179:6, AR183:6, AR233:6, AR252:6, AR239:6, AR204:6, AR282:6, AR177:6, AR104:5, AR174:5, AR277:5, AR309:5, AR264:5, AR269:5, AR228:5, AR243:5, AR197:5, AR207:5, AR312:5, AR226:5, AR275:5, AR192:5, AR219:5, AR196:5, AR270:5, AR212:5, AR293:5, AR237:5, AR238:5, AR253:5, AR236:5, AR218:4, AR268:4, AR262:4, AR261:4, AR267:4, AR234:4, AR246:4, AR201:4, AR283:4, AR258:4, AR191:4, AR296:4, AR171:4, AR254:4, AR213:4, AR272:4, AR230:4, AR308:4, AR255:4, AR231:4, AR235:4, AR289:3, AR199:3, AR061:3, AR291:3, AR297:3, AR286:3, AR288:3, AR205:3, AR222:3, AR263:3, AR227:3, AR193:3, AR200:3, AR214:3, AR290:3, AR033:3, AR294:3, AR203:3, AR256:2, AR295:2, AR285:2, AR232:2, AR287:2, AR189:2, AR195:2, AR224:2, AR225:2, AR216:2, AR188:2, AR311:2, AR260:2, AR190:2, AR242:2, AR210:1, AR172:1, AR170:1, AR211:1 S0052:1
117	HNGND37	839224	127	AR161:7, AR162:7, AR163:7, AR176:6, AR055:5, AR181:5, AR180:5, AR269:5, AR266:5, AR178:5, AR267:5, AR268:5, AR229:5, AR060:4, AR104:4, AR271:4, AR222:4, AR261:4, AR225:4, AR224:4, AR228:4, AR165:4, AR089:4, AR177:4, AR257:4, AR233:4, AR053:4, AR300:4, AR164:4, AR182:4, AR270:4, AR033:4, AR166:4, AR264:4, AR183:3, AR168:3, AR289:3, AR235:3, AR237:3, AR236:3, AR290:3, AR255:3, AR061:3, AR296:3, AR238:3, AR231:3, AR277:3, AR250:3, AR239:3, AR240:3, AR175:3, AR226:3, AR293:3, AR230:3, AR221:3, AR170:3, AR287:3, AR174:3, AR185:3, AR179:3, AR216:3, AR291:3, AR316:3, AR288:3, AR297:3, AR294:3, AR169:3, AR282:3, AR227:2, AR191:2, AR096:2, AR283:2, AR309:2, AR214:2, AR247:2, AR234:2, AR262:2, AR263:2, AR232:2, AR196:2, AR299:2, AR286:2, AR275:2, AR171:2, AR203:2, AR285:2, AR173:2, AR295:2, AR189:2, AR204:2, AR274:2, AR190:2, AR312:2, AR172:2, AR246:2, AR200:2, AR217:2, AR308:2, AR211:2, AR258:2, AR188:2, AR201:2, AR260:2, AR313:2, AR272:2, AR039:2, AR243:1, AR218:1, AR219:1, AR210:1, AR199:1, AR213:1, AR205:1, AR256:1, AR252:1 L0749:4, L0439:3, H0100:2, L0770:2, L0776:2, H0556:1, H0638:1, H0441:1, T0010:1, H0687:1, L0055:1, L0769:1, L0809:1, S0428:1, H0522:1, H0694:1, L0758:1, L0589:1 and L0592:1.
118	HNGOI12	1041375	128	AR225:30, AR223:24, AR221:18, AR224:17, AR215:14, AR168:12, AR214:9, AR222:9, AR216:9, AR171:8, AR217:8, AR266:8, AR172:8, AR176:7, AR269:7, AR182:7, AR288:7, AR180:7, AR245:7, AR289:6, AR161:6, AR162:6, AR204:6, AR255:6, AR197:6, AR270:6, AR183:6, AR297:6, AR163:6, AR178:6, AR268:6, AR181:6, AR282:6, AR236:5, AR231:5, AR039:5, AR293:5, AR207:5, AR179:5, AR294:5, AR201:5, AR295:5, AR198:5, AR169:5, AR240:5, AR286:5, AR261:5, AR229:5, AR165:5, AR205:5, AR170:4, AR285:4, AR233:4, AR309:4, AR290:4, AR257:4, AR177:4, AR055:4, AR175:4, AR246:4, AR300:4, AR287:4, AR256:4, AR173:4, AR243:4, AR271:4, AR267:4, AR235:4, AR264:4, AR164:4, AR263:4, AR247:4, AR313:4, AR166:4, AR277:4, AR262:4, AR060:4, AR238:4, AR260:4, AR191:4, AR291:4, AR316:4, AR258:4, AR239:4, AR053:4, AR296:4, AR228:4, AR174:4, AR250:4, AR199:4, AR096:3, AR192:3, AR230:3, AR237:3, AR196:3, AR193:3, AR234:3, AR283:3, AR104:3, AR203:3, AR190:3, AR272:3, AR200:3, AR253:3, AR189:3, AR061:3, AR185:3, AR311:3, AR275:3, AR226:3, AR299:3, AR089:3, AR227:3, AR188:3, AR312:3, AR232:2, AR219:2, AR274:2, AR033:2, AR195:2, AR212:2, AR213:2, AR211:2, AR218:1, AR242:1, AR210:1, AR308:1 S0428:1
	HNGOI12	838184	249	
	HNGOI12	839283	250	
119	HNHEU93	634851	129	AR313:24, AR173:20, AR162:16, AR161:16, AR163:16, AR165:15, AR247:14, AR164:14, AR166:14, AR175:13, AR258:13,

				AR242:13, AR293:12, AR257:11, AR270:10, AR262:10, AR178:10, AR299:10, AR300:10, AR240:9, AR269:9, AR176:9, AR233:9, AR254:9, AR229:9, AR264:9, AR180:9, AR196:9, AR179:9, AR312:9, AR199:9, AR177:9, AR182:9, AR181:9, AR275:8, AR296:8, AR183:8, AR294:8, AR238:8, AR191:8, AR197:8, AR193:8, AR297:8, AR274:7, AR234:7, AR253:7, AR174:7, AR226:7, AR053:7, AR260:7, AR267:7, AR285:7, AR268:7, AR237:7, AR286:6, AR089:6, AR189:6, AR290:6, AR252:6, AR291:6, AR287:6, AR096:6, AR204:6, AR231:6, AR192:6, AR255:6, AR228:6, AR250:6, AR188:6, AR288:6, AR185:6, AR033:6, AR263:6, AR261:6, AR198:6, AR282:6, AR309:6, AR272:6, AR203:5, AR212:5, AR239:5, AR245:5, AR207:5, AR295:5, AR289:5, AR266:5, AR195:5, AR308:5, AR190:5, AR218:5, AR200:5, AR277:5, AR201:4, AR256:4, AR219:4, AR230:4, AR227:4, AR316:4, AR246:4, AR213:4, AR271:4, AR236:4, AR215:4, AR243:4, AR232:3, AR061:3, AR205:3, AR039:3, AR224:3, AR060:3, AR172:3, AR225:2, AR210:2, AR211:2, AR104:2, AR171:2, AR221:2, AR223:2, AR311:2, AR283:2, AR216:1, AR055:1 S0053:1
120	HNHFM14	664507	130	AR270:26, AR273:17, AR052:17, AR186:12, AR290:12, AR309:11, AR269:10, AR268:9, AR313:8, AR175:7, AR267:7, AR184:6, AR312:6, AR183:5, AR213:5, AR298:5, AR219:5, AR274:4, AR218:4, AR293:4, AR249:4, AR194:4, AR089:4, AR185:4, AR162:3, AR161:3, AR265:3, AR163:3, AR198:3, AR060:3, AR261:3, AR104:3, AR096:3, AR204:3, AR192:3, AR207:3, AR251:3, AR282:3, AR172:3, AR217:3, AR236:3, AR264:3, AR181:3, AR221:3, AR225:2, AR195:2, AR240:2, AR248:2, AR246:2, AR231:2, AR299:2, AR171:2, AR271:2, AR239:2, AR176:2, AR201:2, AR228:2, AR277:2, AR295:2, AR316:2, AR178:2, AR179:2, AR061:2, AR216:2, AR224:2, AR291:2, AR193:2, AR033:2, AR287:2, AR234:2, AR300:1, AR310:1, AR233:1, AR296:1, AR286:1, AR238:1, AR237:1, AR174:1, AR262:1, AR285:1, AR191:1, AR294:1, AR227:1, AR255:1, AR257:1, AR297:1, AR247:1, AR232:1, AR289:1 L0747:5, H0619:4, S0406:4, L0439:4, L0777:4, H0617:2, L0770:2, L0769:2, L0803:2, L0438:2, L3827:2, S0328:2, L0749:2, L0779:2, H0265:1, L3643:1, H0484:1, S0418:1, H0747:1, L3388:1, H0618:1, S0010:1, H0052:1, H0570:1, H0012:1, H0014:1, H0510:1, H0288:1, H0622:1, S0366:1, H0040:1, H0623:1, L0351:1, T0042:1, L0761:1, L0764:1, L0767:1, L0805:1, L0655:1, L0809:1, S0053:1, L3828:1, H0520:1, H0435:1, H0659:1, S3014:1, L0743:1, L0756:1, L0758:1 and H0136:1.
121	HNHNB29	895462	131	AR313:23, AR254:22, AR162:20, AR161:20, AR163:19, AR173:17, AR165:16, AR164:16, AR166:15, AR229:14, AR176:13, AR178:13, AR247:13, AR268:13, AR271:13, AR269:12, AR183:12, AR193:12, AR180:12, AR175:11, AR096:11, AR270:11, AR257:11, AR214:11, AR293:11, AR170:11, AR181:10, AR267:10, AR179:10, AR182:10, AR300:10, AR253:10, AR192:10, AR197:10, AR174:9, AR258:9, AR226:9, AR242:9, AR275:9, AR262:9, AR240:9, AR296:9, AR274:9, AR238:9, AR266:9, AR169:8, AR312:8, AR233:8, AR250:8, AR264:8, AR199:8, AR196:8, AR246:8, AR309:8, AR245:8, AR237:8, AR189:8, AR272:8, AR291:8, AR195:8, AR204:7, AR172:7, AR089:7, AR243:7, AR191:7, AR290:7, AR177:7, AR297:7, AR286:7, AR234:7, AR198:7, AR255:6, AR277:6, AR235:6, AR239:6, AR228:6, AR294:6, AR190:6, AR201:6, AR033:6, AR203:6, AR215:6, AR308:6, AR231:6, AR289:6, AR188:5, AR236:5, AR185:5, AR039:5, AR285:5, AR261:5, AR230:5, AR282:5, AR168:5, AR299:5, AR225:5, AR288:5, AR205:5, AR287:5, AR295:5, AR053:5, AR060:5, AR263:5, AR227:4, AR213:4, AR200:4, AR316:4, AR224:4, AR311:4, AR212:4, AR260:4, AR061:4, AR171:4, AR219:4, AR211:3, AR256:3, AR232:3, AR252:3, AR218:3, AR222:3, AR207:3, AR055:3, AR221:3, AR216:3, AR104:2, AR223:2, AR217:1, AR210:1 S0216:1
122	HNHOD46	843488	132	AR039:32, AR313:28, AR096:21, AR089:19, AR299:16, AR185:11, AR277:11, AR316:11, AR300:10, AR104:10, AR060:9, AR219:8, AR218:8, AR240:7, AR055:7, AR161:6, AR162:6, AR173:6, AR282:6, AR163:6, AR165:6, AR164:6, AR166:6, AR183:5, AR247:5, AR270:5, AR229:5, AR176:4, AR175:4, AR181:4, AR269:4, AR257:4, AR179:4, AR238:4, AR283:4,

				AR178:4, AR196:4, AR293:4, AR309:4, AR262:4, AR268:4, AR250:4, AR182:4, AR174:3, AR236:3, AR199:3, AR177:3, AR213:3, AR230:3, AR234:3, AR171:3, AR291:3, AR296:3, AR233:3, AR258:3, AR255:3, AR286:3, AR180:3, AR191:3, AR189:3, AR237:3, AR297:3, AR312:3, AR261:3, AR294:3, AR295:3, AR168:3, AR053:3, AR263:3, AR226:3, AR274:3, AR287:2, AR225:2, AR188:2, AR231:2, AR308:2, AR203:2, AR267:2, AR239:2, AR285:2, AR289:2, AR033:2, AR169:2, AR275:2, AR227:2, AR266:2, AR264:2, AR290:2, AR224:2, AR200:2, AR190:2, AR243:2, AR311:2, AR228:2, AR212:2, AR222:2, AR216:2, AR272:1, AR172:1, AR211:1, AR260:1, AR235:1, AR061:1 S0216:1
123	HNTBI26	1310821	133	AR195:19, AR214:19, AR194:18, AR225:16, AR223:16, AR164:16, AR165:16, AR281:16, AR166:15, AR224:15, AR172:15, AR216:15, AR215:15, AR202:15, AR161:14, AR162:14, AR222:14, AR221:14, AR199:14, AR217:14, AR280:14, AR244:14, AR169:14, AR163:14, AR206:14, AR171:13, AR168:13, AR315:13, AR207:12, AR235:12, AR211:12, AR170:12, AR246:12, AR268:11, AR192:11, AR265:11, AR197:11, AR263:11, AR314:11, AR196:11, AR311:10, AR243:10, AR241:10, AR205:10, AR245:10, AR264:10, AR297:9, AR242:9, AR288:9, AR198:9, AR212:9, AR191:9, AR308:9, AR213:8, AR269:8, AR273:8, AR309:8, AR270:8, AR310:8, AR290:8, AR053:8, AR272:8, AR275:8, AR200:8, AR252:8, AR189:8, AR173:8, AR261:8, AR289:8, AR180:8, AR089:8, AR210:7, AR312:7, AR188:7, AR251:7, AR234:7, AR183:7, AR284:7, AR271:7, AR236:7, AR190:7, AR238:7, AR295:7, AR181:7, AR253:7, AR291:7, AR282:7, AR248:7, AR247:7, AR266:7, AR285:7, AR283:7, AR193:7, AR177:7, AR182:7, AR033:7, AR250:7, AR174:7, AR204:7, AR176:6, AR240:6, AR274:6, AR254:6, AR052:6, AR060:6, AR286:6, AR239:6, AR175:6, AR249:6, AR299:6, AR277:6, AR257:6, AR218:6, AR316:6, AR061:5, AR298:5, AR096:5, AR287:5, AR178:5, AR300:5, AR255:5, AR231:5, AR185:5, AR296:5, AR203:5, AR313:5, AR292:5, AR201:5, AR232:5, AR039:5, AR186:5, AR227:5, AR055:5, AR219:5, AR258:5, AR267:5, AR294:5, AR262:5, AR293:4, AR229:4, AR179:4, AR260:4, AR226:4, AR237:4, AR228:4, AR233:4, AR104:4, AR184:3, AR230:3, AR256:3, AR259:2 H0124:23, L0774:4, L0740:3, S0212:2, S0360:2, L3388:2, L0659:2, L0757:2, S0436:2, H0170:1, H0713:1, H0580:1, S0045:1, H0393:1, S0220:1, H0333:1, H0643:1, H0574:1, H0013:1, S0280:1, H0581:1, H0544:1, H0150:1, H0059:1, H0509:1, L0369:1, L0640:1, L0521:1, L0363:1, L0775:1, L0654:1, L0776:1, L0559:1, L0384:1, L0790:1, L0664:1, L2258:1, L2260:1, H0519:1, S0027:1, S0206:1, L0747:1, L0749:1, L0780:1, L0731:1, L0759:1 and H0542:1.
	HNTBI26	796807	251	
	HNTBI26	590738	252	
124	HNTBL27	545534	134	AR218:6, AR240:5, AR282:5, AR277:5, AR316:5, AR096:4, AR219:4, AR185:4, AR104:4, AR300:3, AR299:3, AR060:3, AR283:3, AR055:3, AR313:3, AR089:3, AR039:3 L0794:3, L0663:2, S0360:1, H0042:1, H0253:1, H0150:1, H0633:1, S0142:1, H0538:1, L0804:1, L0790:1, L0791:1, L0666:1, L0664:1, L0665:1, H0519:1, L0747:1, L0749:1, L0779:1, L0777:1, L0755:1 and L0731:1.
125	HNTCE26	1160395	135	AR291:7, AR164:5, AR295:5, AR296:5, AR285:5, AR166:5, AR165:5, AR170:4, AR297:4, AR287:4, AR162:4, AR286:4, AR161:4, AR235:4, AR311:4, AR257:4, AR288:4, AR223:4, AR225:4, AR053:4, AR089:4, AR060:4, AR308:4, AR261:4, AR169:4, AR262:4, AR176:4, AR096:4, AR264:4, AR266:3, AR283:3, AR199:3, AR246:3, AR178:3, AR289:3, AR214:3, AR267:3, AR205:3, AR269:3, AR312:3, AR245:3, AR263:3, AR195:3, AR196:3, AR175:3, AR255:3, AR293:3, AR236:3, AR270:3, AR277:3, AR173:3, AR104:3, AR272:3, AR188:3, AR183:3, AR294:3, AR268:3, AR224:3, AR258:3, AR242:3, AR182:3, AR238:3, AR189:3, AR193:3, AR316:3, AR191:3, AR180:3, AR174:3, AR163:2, AR197:2, AR253:2, AR210:2, AR290:2, AR200:2, AR190:2, AR203:2, AR217:2, AR247:2, AR181:2, AR299:2, AR185:2, AR260:2, AR211:2, AR282:2,

				AR313:2, AR309:2, AR254:2, AR256:2, AR033:2, AR201:2, AR179:2, AR213:2, AR227:2, AR171:2, AR237:2, AR168:2, AR222:2, AR300:2, AR240:2, AR243:2, AR234:2, AR274:2, AR219:2, AR204:2, AR239:2, AR218:2, AR233:1, AR231:1, AR177:1, AR216:1, AR172:1, AR212:1, AR055:1, AR061:1, AR230:1, AR232:1, AR226:1 H0580:5, L0754:5, H0615:4, L0805:4, L0748:4, L0731:4, H0031:3, S0440:3, L0659:3, L0758:3, L2346:2, S0278:2, L0804:2, L0809:2, H0547:2, H0352:2, H0657:1, H0656:1, S0418:1, S0442:1, S0444:1, L3649:1, H0741:1, H0645:1, H0574:1, H0486:1, L3521:1, H0013:1, S0010:1, H0327:1, H0046:1, L0041:1, H0510:1, S0214:1, H0328:1, H0030:1, H0553:1, H0644:1, H0032:1, S0344:1, S0002:1, L0369:1, L0667:1, L0364:1, L0794:1, L0803:1, L0775:1, L0776:1, L0789:1, L0666:1, L0663:1, L2653:1, L0438:1, H0519:1, H0670:1, H0521:1, L0744:1, L0439:1, L0747:1, L0779:1, L0591:1 and L3374:1.
	HNTCE26	853373	253	
126	HNTNI01	1352285	136	AR207:15, AR263:12, AR169:11, AR311:11, AR212:10, AR198:10, AR264:10, AR235:10, AR252:9, AR168:9, AR223:9, AR224:9, AR089:9, AR053:8, AR215:8, AR172:8, AR161:8, AR162:8, AR214:8, AR222:8, AR163:8, AR309:8, AR165:8, AR205:8, AR192:8, AR164:8, AR170:8, AR221:7, AR166:7, AR216:7, AR242:7, AR282:7, AR308:7, AR195:7, AR171:7, AR039:7, AR213:7, AR261:7, AR312:7, AR245:6, AR254:6, AR295:6, AR225:6, AR033:6, AR197:6, AR288:6, AR217:6, AR060:5, AR196:5, AR274:5, AR096:5, AR246:5, AR271:5, AR291:5, AR193:5, AR316:5, AR286:5, AR277:5, AR283:5, AR299:5, AR178:5, AR272:5, AR275:5, AR236:4, AR243:4, AR285:4, AR240:4, AR104:4, AR313:4, AR185:4, AR176:4, AR296:4, AR297:4, AR204:4, AR287:4, AR210:4, AR055:4, AR177:4, AR253:4, AR183:4, AR181:4, AR290:4, AR247:4, AR269:4, AR258:4, AR289:4, AR257:4, AR201:4, AR174:3, AR238:3, AR200:3, AR262:3, AR300:3, AR175:3, AR199:3, AR294:3, AR255:3, AR188:3, AR268:3, AR180:3, AR293:3, AR211:3, AR173:3, AR266:3, AR250:3, AR270:3, AR061:3, AR189:3, AR179:3, AR267:3, AR239:3, AR182:3, AR190:3, AR227:2, AR231:2, AR234:2, AR256:2, AR219:2, AR237:2, AR203:2, AR191:2, AR229:2, AR226:2, AR230:2, AR232:2, AR260:2, AR233:2, AR218:2, AR228:1 L0747:5, H0545:3, H0520:3, L0439:3, L0803:2, L0790:2, H0547:2, L0740:2, L0751:2, L0779:2, L0759:2, L0593:2, H0170:1, S0005:1, H0485:1, H0013:1, L0564:1, L0770:1, L0794:1, L0809:1, H0519:1, S0378:1, L0756:1, L0777:1 and H0667:1.
	HNTNI01	699848	254	
127	HODDF13	684307	137	AR312:21, AR308:20, AR205:19, AR253:19, AR250:19, AR309:19, AR264:18, AR311:16, AR212:16, AR213:15, AR218:14, AR096:14, AR272:14, AR313:14, AR263:14, AR161:13, AR162:13, AR163:13, AR165:13, AR164:12, AR175:12, AR053:12, AR219:12, AR089:12, AR166:12, AR246:12, AR178:11, AR270:11, AR254:11, AR271:11, AR173:11, AR274:10, AR039:10, AR192:10, AR174:10, AR176:10, AR282:10, AR216:10, AR189:10, AR193:10, AR183:9, AR221:9, AR268:9, AR191:9, AR252:9, AR210:9, AR245:9, AR172:9, AR269:9, AR290:9, AR197:9, AR180:9, AR242:8, AR217:8, AR224:8, AR182:8, AR316:8, AR215:8, AR293:8, AR181:8, AR288:8, AR179:8, AR267:8, AR060:8, AR190:8, AR171:7, AR247:7, AR201:7, AR297:7, AR195:7, AR240:7, AR185:7, AR222:7, AR177:7, AR199:6, AR170:6, AR295:6, AR291:6, AR188:6, AR198:6, AR211:6, AR243:6, AR266:6, AR275:6, AR104:6, AR299:6, AR204:6, AR229:5, AR300:5, AR237:5, AR294:5, AR169:5, AR285:5, AR225:5, AR033:5, AR296:5, AR286:5, AR287:5, AR261:5, AR238:5, AR168:5, AR289:4, AR231:4, AR230:4, AR223:4, AR277:4, AR214:4, AR226:4, AR228:4, AR203:4, AR239:4, AR196:4, AR255:4, AR234:4, AR235:4, AR233:4, AR262:4, AR260:3, AR236:3, AR257:3, AR061:3, AR256:3, AR232:3, AR200:3, AR227:3, AR258:3, AR283:3, AR055:2, AR207:2 H0328:1
128	HODDN92	422913	138	AR161:4, AR162:4, AR163:4, AR192:4, AR165:4, AR308:4, AR264:4, AR176:4, AR311:3, AR164:3, AR309:3, AR166:3,

				AR312:3, AR213:3, AR214:3, AR193:3, AR225:3, AR313:3, AR096:3, AR089:3, AR270:3, AR172:3, AR235:3, AR299:2, AR201:2, AR291:2, AR104:2, AR269:2, AR195:2, AR294:2, AR169:2, AR215:2, AR290:2, AR224:2, AR173:2, AR060:2, AR288:2, AR282:2, AR285:2, AR271:2, AR185:2, AR175:2, AR039:2, AR275:2, AR277:2, AR211:2, AR268:2, AR316:2, AR190:2, AR267:2, AR274:2, AR272:2, AR171:2, AR287:2, AR221:2, AR237:2, AR189:1, AR289:1, AR217:1, AR300:1, AR247:1, AR255:1, AR262:1, AR257:1, AR183:1, AR286:1, AR236:1, AR256:1, AR293:1, AR254:1, AR295:1, AR178:1, AR297:1, AR238:1, AR296:1, AR168:1 L0758:14, H0457:10, H0556:5, S0114:5, L0748:5, L0756:5, H0657:4, H0620:4, H0328:4, H0591:4, L0754:4, L0779:4, H0589:3, L0532:3, H0445:3, H0341:2, H0580:2, H0208:2, H0619:2, H0486:2, H0013:2, L0471:2, H0024:2, H0673:2, H0674:2, H0038:2, H0264:2, H0561:2, L0803:2, L0606:2, L0519:2, S0216:2, L0749:2, L0777:2, L0589:2, H0171:1, S0218:1, S0212:1, H0255:1, H0305:1, S0358:1, S0444:1, H0329:1, L0717:1, S0222:1, H0370:1, H0438:1, H0586:1, H0574:1, H0632:1, H0581:1, H0310:1, H0544:1, H0009:1, H0123:1, H0350:1, S0003:1, H0252:1, H0615:1, H0644:1, H0598:1, S0036:1, H0090:1, H0063:1, S0038:1, H0625:1, H0538:1, L0373:1, L0794:1, L0650:1, L0774:1, L0805:1, L0559:1, L0558:1, L0659:1, L0526:1, H0144:1, H0520:1, H0696:1, S0206:1, S0434:1, S0011:1, S0026:1, H0543:1 and H0423:1.
129	HOFMQ33	1184465	139	AR205:90, AR212:77, AR245:75, AR274:68, AR272:67, AR216:65, AR246:62, AR252:60, AR308:59, AR213:59, AR214:55, AR312:54, AR215:54, AR197:50, AR309:50, AR254:50, AR053:50, AR217:49, AR171:49, AR221:49, AR195:48, AR311:45, AR225:45, AR223:44, AR264:44, AR170:44, AR189:44, AR199:43, AR210:43, AR263:43, AR168:43, AR247:43, AR243:41, AR224:41, AR172:41, AR253:40, AR222:40, AR169:39, AR164:37, AR250:37, AR174:37, AR271:36, AR166:36, AR198:36, AR165:36, AR201:34, AR188:34, AR162:34, AR190:32, AR163:32, AR242:32, AR161:32, AR204:29, AR193:28, AR173:27, AR192:26, AR313:26, AR236:25, AR291:24, AR177:24, AR275:24, AR290:24, AR256:23, AR039:22, AR262:22, AR096:22, AR191:22, AR240:22, AR219:22, AR200:22, AR185:22, AR179:21, AR218:21, AR089:21, AR211:20, AR300:20, AR288:20, AR175:20, AR297:20, AR289:20, AR295:19, AR255:19, AR261:19, AR299:19, AR203:19, AR207:19, AR293:18, AR196:18, AR268:17, AR237:17, AR296:17, AR258:17, AR282:16, AR316:16, AR285:16, AR231:15, AR269:15, AR257:15, AR178:14, AR234:14, AR287:14, AR181:14, AR230:14, AR033:14, AR260:14, AR267:14, AR061:14, AR233:14, AR239:14, AR183:13, AR266:13, AR270:13, AR229:13, AR286:13, AR277:12, AR180:12, AR060:12, AR238:12, AR226:12, AR232:12, AR176:12, AR227:11, AR294:11, AR228:10, AR283:9, AR235:9, AR182:8, AR104:7, AR055:5 H0415:1
	HOFMQ33	919896	255	
	HOFMQ33	906694	256	
	HOFMQ33	902639	257	
	HOFMQ33	702186	258	
130	HOFOC73	931871	140	AR294:16, AR169:6, AR245:6, AR192:6, AR170:6, AR195:6, AR263:5, AR039:5, AR164:4, AR165:4, AR215:4, AR053:4, AR266:4, AR172:4, AR161:4, AR212:4, AR162:4, AR089:4, AR222:4, AR223:4, AR213:4, AR274:4, AR261:3, AR254:3, AR272:3, AR221:3, AR264:3, AR171:3, AR205:3, AR225:3, AR168:3, AR193:3, AR060:3, AR217:3, AR277:3, AR096:3, AR224:3, AR282:3, AR175:3, AR308:3, AR312:3, AR214:3, AR196:3, AR288:3, AR235:2, AR180:2, AR197:2, AR311:2, AR283:2, AR299:2, AR240:2, AR316:2, AR295:2, AR216:2, AR297:2, AR270:2, AR236:2, AR291:2, AR104:2, AR055:2, AR188:2, AR238:2, AR201:2, AR300:2, AR246:2, AR191:2, AR293:2, AR243:2, AR309:2, AR176:2, AR247:2, AR289:2,

				AR257:2, AR174:2, AR285:2, AR173:2, AR185:2, AR200:2, AR178:2, AR190:2, AR267:2, AR210:2, AR177:2, AR268:2, AR290:2, AR233:2, AR275:2, AR203:2, AR189:2, AR181:1, AR286:1, AR287:1, AR033:1, AR313:1, AR296:1, AR199:1, AR228:1, AR227:1, AR231:1, AR262:1, AR237:1, AR252:1, AR218:1, AR242:1, AR207:1, AR234:1, AR226:1, AR258:1 L0740:8, L0748:7, L0749:7, L0752:4, L0588:4, L0750:3, L0757:3, L0759:3, S0436:3, S0358:2, H0415:2, H0090:2, L0774:2, L0805:2, L0776:2, L0783:2, L0809:2, L0751:2, L0747:2, S0040:1, S0420:1, S0442:1, S0376:1, S0360:1, S0408:1, H0580:1, H0550:1, L0586:1, H0036:1, S0346:1, H0581:1, T0110:1, H0597:1, H0530:1, H0123:1, H0083:1, H0354:1, H0510:1, T0069:1, H0560:1, S0210:1, L0763:1, L0637:1, L0646:1, L0800:1, L0771:1, L0773:1, L0775:1, L0659:1, L0789:1, L0666:1, H0691:1, H0576:1, H0478:1, H0626:1, L0731:1, H0444:1, L0592:1 and S0242:1.
	HOFOC73	907073	259	
	HOFOC73	907072	260	
	HOFOC73	878863	261	
131	HOQBJ82	1352356	141	AR207:16, AR197:15, AR309:14, AR195:13, AR311:13, AR263:13, AR224:13, AR264:13, AR245:13, AR223:12, AR235:12, AR253:12, AR252:12, AR246:11, AR201:11, AR222:10, AR170:10, AR171:10, AR221:10, AR053:10, AR312:10, AR172:9, AR308:9, AR198:9, AR169:9, AR225:9, AR168:9, AR242:9, AR214:9, AR215:9, AR177:9, AR192:9, AR212:9, AR272:9, AR165:9, AR295:8, AR196:8, AR089:8, AR166:8, AR271:8, AR261:8, AR216:8, AR164:8, AR210:8, AR200:7, AR199:7, AR213:7, AR218:7, AR277:7, AR254:7, AR288:7, AR176:7, AR219:7, AR316:7, AR193:7, AR274:7, AR240:7, AR285:7, AR181:7, AR236:7, AR217:7, AR282:7, AR204:7, AR178:7, AR211:6, AR291:6, AR275:6, AR286:6, AR162:6, AR161:6, AR287:6, AR060:6, AR247:6, AR203:6, AR096:6, AR250:6, AR163:6, AR243:6, AR188:6, AR183:6, AR033:6, AR205:6, AR266:6, AR191:6, AR268:6, AR174:6, AR180:6, AR189:6, AR293:5, AR229:5, AR104:5, AR175:5, AR289:5, AR055:5, AR270:5, AR299:5, AR297:5, AR296:5, AR039:5, AR313:5, AR300:5, AR231:5, AR262:5, AR234:5, AR290:5, AR267:5, AR257:5, AR239:5, AR233:4, AR226:4, AR238:4, AR237:4, AR269:4, AR258:4, AR173:4, AR185:4, AR228:4, AR294:4, AR283:4, AR182:4, AR230:4, AR061:4, AR255:4, AR190:4, AR232:4, AR179:4, AR256:4, AR260:4, AR227:3 L0766:12, L0758:7, H0616:4, L0439:4, L0754:4, L0747:4, L0779:4, L0777:4, L0601:4, H0657:3, H0656:3, H0081:3, H0031:3, H0038:3, S0222:2, H0455:2, H0618:2, H0617:2, T0042:2, H0494:2, S0210:2, H0529:2, L0769:2, L0662:2, L0794:2, L0665:2, H0445:2, H0543:2, H0170:1, H0394:1, H0556:1, T0002:1, S0029:1, H0662:1, S0358:1, S0045:1, S0046:1, S0140:1, L0717:1, H0370:1, H0392:1, H0497:1, H0574:1, H0253:1, H0318:1, H0597:1, H0544:1, H0545:1, H0178:1, L0157:1, L0471:1, S0050:1, H0014:1, H0051:1, T0010:1, H0408:1, H0266:1, H0188:1, H0290:1, S0022:1, H0135:1, H0090:1, H0040:1, H0634:1, H0264:1, S0448:1, H0641:1, S0142:1, S0344:1, L0770:1, L0637:1, L0645:1, L0771:1, L0521:1, L0768:1, L0803:1, L0806:1, L0805:1, L0652:1, L0653:1, L0776:1, L0655:1, L0629:1, L0659:1, L0789:1, L0791:1, L0663:1, L0664:1, H0519:1, H0682:1, H0539:1, H0521:1, H0522:1, H0134:1, H0214:1, L0749:1, L0750:1, H0667:1, H0542:1, H0423:1 and H0422:1.
	HOQBJ82	858338	262	
	HOQBJ82	857453	263	
132	HOSBY40	589431	142	AR197:6, AR309:6, AR250:5, AR176:5, AR245:4, AR169:4, AR161:4, AR162:4, AR277:4, AR163:4, AR201:4, AR282:4, AR253:4, AR198:4, AR177:4, AR229:3, AR272:3, AR181:3, AR089:3, AR299:3, AR193:3, AR264:3, AR269:3, AR239:3, AR190:3, AR189:3, AR246:3, AR233:3, AR237:3, AR195:3, AR257:3, AR238:3, AR300:3, AR313:3, AR165:3, AR270:3,

				AR172:3, AR166:3, AR271:3, AR275:3, AR255:3, AR240:3, AR207:2, AR274:2, AR216:2, AR228:2, AR312:2, AR215:2, AR183:2, AR196:2, AR226:2, AR311:2, AR096:2, AR203:2, AR262:2, AR191:2, AR247:2, AR060:2, AR268:2, AR316:2, AR199:2, AR188:2, AR243:2, AR205:2, AR261:2, AR231:2, AR178:2, AR180:2, AR227:2, AR223:2, AR263:2, AR232:2, AR266:2, AR222:2, AR061:2, AR164:2, AR258:2, AR217:1, AR200:1, AR213:1, AR224:1, AR174:1, AR283:1, AR182:1, AR267:1, AR171:1, AR185:1, AR234:1, AR192:1, AR297:1, AR170:1 S0418:1, H0393:1, S0003:1, L0766:1, L0804:1 and S0052:1.
133	HOSDJ25	854234	143	AR207:16, AR263:14, AR235:13, AR224:13, AR225:13, AR309:12, AR196:12, AR311:12, AR214:12, AR223:12, AR172:12, AR246:11, AR168:11, AR217:11, AR264:11, AR171:11, AR215:11, AR170:11, AR291:10, AR221:10, AR222:10, AR295:10, AR288:10, AR195:10, AR039:10, AR277:10, AR192:10, AR197:10, AR161:10, AR169:10, AR162:10, AR261:9, AR216:9, AR163:9, AR165:9, AR205:9, AR210:9, AR236:9, AR177:9, AR198:9, AR164:9, AR089:9, AR191:9, AR245:9, AR201:9, AR242:9, AR212:9, AR166:8, AR188:8, AR285:8, AR240:8, AR174:8, AR252:8, AR290:8, AR271:8, AR250:8, AR260:8, AR176:8, AR219:8, AR282:8, AR200:8, AR312:8, AR316:8, AR253:8, AR181:8, AR297:7, AR060:7, AR308:7, AR096:7, AR199:7, AR289:7, AR286:7, AR287:7, AR293:7, AR213:7, AR262:7, AR313:7, AR180:7, AR300:7, AR269:7, AR257:7, AR193:7, AR231:6, AR275:6, AR296:6, AR258:6, AR255:6, AR175:6, AR218:6, AR190:6, AR053:6, AR266:6, AR178:6, AR270:6, AR268:6, AR233:6, AR243:6, AR182:6, AR189:6, AR294:6, AR104:6, AR185:6, AR239:6, AR173:5, AR179:5, AR204:5, AR272:5, AR256:5, AR299:5, AR274:5, AR247:5, AR033:5, AR183:5, AR211:5, AR229:5, AR267:5, AR234:5, AR237:5, AR055:5, AR238:4, AR228:4, AR230:4, AR203:4, AR061:4, AR283:4, AR232:4, AR226:4, AR227:3, AR254:3 L0754:4, L0749:4, L0659:3, L0755:3, S0356:2, L0803:2, L0750:2, L0779:2, L0599:2, S0029:1, H0661:1, S0354:1, H0642:1, T0040:1, L0021:1, H0599:1, H0510:1, S0003:1, H0674:1, H0316:1, H0623:1, S0422:1, L0794:1, L0522:1, L0774:1, L0526:1, L0809:1, H0520:1, H0659:1, H0670:1, L0752:1, L0608:1 and S0242:1.
	HOSDJ25	566845	264	
134	HPEAD79	520202	144	AR277:24, AR176:5, AR039:5, AR162:5, AR205:5, AR161:5, AR235:5, AR163:5, AR282:5, AR309:5, AR168:4, AR223:4, AR228:4, AR181:4, AR266:4, AR182:4, AR269:4, AR229:4, AR257:3, AR233:3, AR272:3, AR178:3, AR180:3, AR165:3, AR264:3, AR261:3, AR268:3, AR195:3, AR164:3, AR275:3, AR166:3, AR267:3, AR183:3, AR196:3, AR238:3, AR237:3, AR236:3, AR316:3, AR171:3, AR170:3, AR179:3, AR245:3, AR060:3, AR262:3, AR193:3, AR177:3, AR255:3, AR242:3, AR289:3, AR201:3, AR230:3, AR311:3, AR254:3, AR215:2, AR290:2, AR294:2, AR204:2, AR216:2, AR231:2, AR287:2, AR299:2, AR288:2, AR227:2, AR300:2, AR033:2, AR089:2, AR191:2, AR239:2, AR173:2, AR271:2, AR225:2, AR270:2, AR295:2, AR293:2, AR296:2, AR234:2, AR185:2, AR285:2, AR214:2, AR226:2, AR274:2, AR190:2, AR203:2, AR096:2, AR199:2, AR189:2, AR247:2, AR297:2, AR200:2, AR217:2, AR246:2, AR055:2, AR175:2, AR211:2, AR232:2, AR061:2, AR283:2, AR286:2, AR053:1, AR222:1, AR263:1, AR256:1, AR260:1, AR258:1, AR210:1, AR291:1, AR188:1, AR174:1, AR312:1, AR252:1, AR224:1, AR219:1 H0165:1
135	HPIBO15	1310868	145	AR240:10, AR211:10, AR178:9, AR270:8, AR221:8, AR295:7, AR235:7, AR161:7, AR162:7, AR189:7, AR163:7, AR288:7, AR255:6, AR191:6, AR175:6, AR293:6, AR096:6, AR183:6, AR182:6, AR188:6, AR269:5, AR236:5, AR190:5, AR173:5, AR180:5, AR165:5, AR174:5, AR290:5, AR164:5, AR274:5, AR166:5, AR060:5, AR261:5, AR179:5, AR203:5, AR195:5, AR222:5, AR055:4, AR193:4, AR181:4, AR297:4, AR291:4, AR171:4, AR197:4, AR168:4, AR289:4, AR266:4, AR268:4, AR296:4, AR262:4, AR287:4, AR104:4, AR196:4, AR267:4, AR247:4, AR177:4, AR299:4, AR176:4, AR033:4, AR246:4,

				AR172:4, AR225:3, AR263:3, AR286:3, AR275:3, AR217:3, AR170:3, AR316:3, AR294:3, AR285:3, AR308:3, AR228:3, AR300:3, AR282:3, AR089:3, AR257:3, AR277:3, AR214:3, AR238:3, AR224:3, AR245:3, AR233:3, AR210:3, AR272:3, AR201:3, AR254:3, AR309:3, AR311:3, AR243:3, AR264:3, AR212:3, AR215:3, AR185:3, AR312:3, AR260:3, AR213:3, AR313:3, AR053:2, AR256:2, AR200:2, AR237:2, AR231:2, AR283:2, AR229:2, AR061:2, AR239:2, AR216:2, AR227:2, AR232:2, AR226:2, AR258:2, AR234:2, AR230:2, AR271:2, AR199:2, AR039:1, AR223:1 L0747:8, L0749:5, L0755:5, H0013:3, L0769:3, L0731:3, S0212:2, L0770:2, L0803:2, H0144:2, L0756:2, H0624:1, H0171:1, S0282:1, H0776:1, H0592:1, H0427:1, H0575:1, H0041:1, H0124:1, H0163:1, H0038:1, L0637:1, L0774:1, L0775:1, L0791:1, H0648:1, H0756:1, S0028:1, L0439:1, L0777:1 and S0436:1.
	HPIBO15	590741	265	
136	HPJBI33	685699	146	AR161:12, AR162:12, AR163:12, AR313:8, AR165:8, AR229:8, AR164:8, AR166:7, AR275:6, AR247:6, AR180:5, AR264:5, AR270:5, AR173:5, AR233:5, AR237:5, AR174:5, AR274:5, AR176:5, AR181:5, AR177:5, AR246:5, AR240:5, AR312:4, AR263:4, AR234:4, AR309:4, AR183:4, AR096:4, AR179:4, AR185:4, AR182:4, AR238:4, AR269:4, AR178:4, AR282:4, AR293:4, AR272:3, AR231:3, AR296:3, AR268:3, AR196:3, AR230:3, AR104:3, AR226:3, AR170:3, AR089:3, AR300:3, AR228:3, AR261:3, AR175:3, AR297:3, AR236:2, AR217:2, AR291:2, AR311:2, AR169:2, AR316:2, AR255:2, AR033:2, AR295:2, AR294:2, AR191:2, AR267:2, AR168:2, AR171:2, AR277:2, AR286:2, AR290:2, AR262:2, AR199:2, AR227:2, AR189:2, AR239:2, AR203:2, AR257:2, AR285:2, AR223:2, AR299:2, AR266:2, AR060:2, AR287:2, AR214:2, AR190:1, AR200:1, AR061:1, AR308:1, AR216:1, AR213:1, AR224:1, AR195:1, AR289:1, AR055:1 S0152:1
137	HPJBK12	1011467	147	AR215:5, AR197:4, AR039:4, AR309:4, AR245:4, AR161:3, AR162:3, AR163:3, AR204:3, AR165:3, AR225:3, AR169:3, AR264:3, AR282:3, AR272:3, AR089:3, AR180:3, AR213:3, AR172:3, AR253:2, AR166:2, AR212:2, AR193:2, AR252:2, AR271:2, AR312:2, AR275:2, AR164:2, AR060:2, AR240:2, AR216:2, AR266:2, AR201:2, AR205:2, AR183:2, AR176:2, AR195:2, AR223:2, AR283:2, AR277:1, AR311:1, AR247:1, AR313:1, AR242:1, AR199:1, AR299:1, AR316:1, AR188:1, AR104:1, AR168:1, AR185:1, AR291:1, AR287:1, AR231:1, AR294:1, AR230:1, AR096:1 S0152:2
	HPJBK12	525375	266	
	HPJBK12	796925	267	
	HPJBK12	699587	268	
138	HPMDK28	846357	148	AR055:9, AR089:9, AR218:7, AR060:7, AR104:7, AR219:7, AR299:6, AR096:6, AR185:5, AR316:4, AR313:4, AR180:4, AR039:4, AR282:4, AR283:3, AR198:3, AR169:3, AR165:3, AR235:3, AR242:2, AR207:2, AR300:2, AR217:2, AR223:2, AR277:2, AR286:2, AR270:2, AR224:2, AR263:2, AR163:2, AR161:2, AR240:2, AR166:2, AR289:2, AR272:1, AR164:1, AR172:1, AR261:1, AR252:1, AR269:1, AR295:1, AR170:1, AR297:1, AR177:1 S0358:5, L0809:4, L0742:4, L0743:4, L0590:4, H0543:4, S0360:3, H0031:3, S0422:3, L0763:3, L0764:3, L0766:3, L0754:3, H0716:2, H0333:2, H0266:2, H0617:2, L4497:2, L0769:2, L0776:2, H0658:2, H0696:2, L0748:2, L0749:2, H0445:2, S0434:2, S0110:1, H0663:1, L0481:1, H0730:1, H0747:1, H0411:1, H0431:1, H0370:1, H0574:1, H0632:1, L2490:1, H0253:1, H0052:1, H0546:1, H0545:1, H0150:1, H0123:1, H0012:1, S0050:1, S0051:1, H0188:1, S0003:1, H0428:1, T0006:1, H0606:1, H0673:1, H0090:1, H0040:1, H0412:1, T0069:1, S0112:1, S0344:1, H0538:1, H0529:1, L0770:1, L0761:1, L0662:1, L0768:1, L0794:1, L0560:1, L0775:1, L0806:1, L0517:1, L0540:1, L0384:1, L5622:1, L0666:1, L0665:1, L2260:1, L2654:1, S0374:1, H0684:1, L3832:1, S0004:1, S0390:1,

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	HPMDK28	639118	269	
139	HPRAL78	1352342	149	AR104:11, AR089:10, AR060:9, AR283:7, AR277:7, AR039:6, AR055:6, AR316:6, AR096:6, AR219:6, AR263:5, AR299:5, AR218:5, AR313:5, AR185:5, AR240:5, AR282:5, AR206:3, AR204:3, AR300:2, AR312:2, AR291:2, AR251:2, AR246:2, AR052:2, AR184:2, AR202:2, AR290:2, AR232:2, AR295:2, AR238:2, AR237:2, AR298:2, AR270:2, AR309:2, AR292:2, AR268:2, AR285:1, AR177:1, AR310:1, AR182:1, AR213:1, AR226:1, AR053:1, AR186:1, AR175:1, AR289:1, AR205:1, AR183:1, AR233:1, AR294:1, AR284:1, AR229:1 H0694:5, L0759:5, L0766:4, H0261:3, S0222:3, H0486:3, H0052:3, L0731:3, L3316:2, H0252:2, L0764:2, L0662:2, L0775:2, L0657:2, L0659:2, L0530:2, L0666:2, L0748:2, L0439:2, L0750:2, L0588:2, L0594:2, H0224:1, H0717:1, H0656:1, S0001:1, S0360:1, S0408:1, H0729:1, S0045:1, H0619:1, L3388:1, H0592:1, H0587:1, H0333:1, S0474:1, H0014:1, L0163:1, H0051:1, H0355:1, T0006:1, H0644:1, H0032:1, H0212:1, L0456:1, H0124:1, H0708:1, S0036:1, H0038:1, H0616:1, H0087:1, H0059:1, H0280:1, S0440:1, S0150:1, H0633:1, L0369:1, L0763:1, L0769:1, L0638:1, L0637:1, L5566:1, L0761:1, L0772:1, L0648:1, L0803:1, L0650:1, L0805:1, L0809:1, L0647:1, L0665:1, H0539:1, H0521:1, H0696:1, H0555:1, L0754:1, L0749:1, L0753:1, L0755:1, L0757:1, L0605:1, L0599:1 and L3352:1.
	HPRAL78	844216	270	
	HPRAL78	484735	271	
140	HRABA80	882176	150	AR060:929, AR104:796, AR089:725, AR055:678, AR299:627, AR283:625, AR282:494, AR185:464, AR096:462, AR316:387, AR039:363, AR240:317, AR277:285, AR300:278, AR218:153, AR313:152, AR219:140, AR242:4, AR221:3, AR217:2, AR291:2, AR172:2, AR205:2, AR163:2, AR165:2, AR178:2, AR161:2, AR168:2, AR166:2, AR164:1, AR171:1, AR195:1, AR268:1, AR180:1, AR266:1, AR215:1, AR234:1, AR230:1, AR257:1, AR199:1, AR270:1, AR179:1 H0555:1
	HRABA80	588460	272	
141	HRACD15	871221	151	AR193:12, AR165:11, AR164:11, AR166:10, AR299:10, AR313:9, AR162:9, AR161:9, AR246:9, AR163:9, AR205:9, AR312:9, AR311:9, AR089:8, AR243:8, AR245:8, AR096:8, AR195:8, AR242:7, AR176:7, AR270:7, AR291:7, AR212:7, AR297:7, AR264:7, AR288:7, AR199:7, AR197:7, AR282:7, AR300:6, AR240:6, AR272:6, AR196:6, AR285:6, AR275:6, AR201:6, AR200:6, AR263:6, AR213:6, AR229:6, AR221:6, AR225:6, AR183:6, AR266:6, AR268:5, AR293:5, AR283:5, AR255:5, AR104:5, AR247:5, AR274:5, AR308:5, AR180:5, AR262:5, AR295:5, AR236:5, AR316:5, AR254:5, AR053:5, AR191:5, AR215:5, AR287:5, AR277:5, AR203:5, AR238:5, AR188:5, AR223:5, AR039:5, AR235:5, AR269:4, AR261:4, AR189:4, AR309:4, AR289:4, AR060:4, AR258:4, AR182:4, AR175:4, AR294:4, AR210:4, AR185:4, AR286:4, AR174:4, AR178:4, AR198:4, AR192:4, AR257:4, AR177:4, AR190:4, AR290:4, AR173:4, AR179:4, AR033:4, AR296:3, AR214:3, AR217:3, AR181:3, AR267:3, AR170:3, AR256:3, AR231:3, AR224:3, AR253:3, AR234:3, AR230:3, AR239:3, AR260:3, AR237:3, AR252:3, AR250:3, AR233:3, AR216:3, AR204:2, AR226:2, AR227:2, AR232:2, AR061:2, AR228:2, AR211:2, AR171:2, AR222:2, AR172:2, AR168:2, AR055:2, AR207:1, AR218:1 H0556:15, H0265:8, L0751:8, H0617:7, L0662:7, L0766:5, L0809:5, H0040:4, H0494:4, S0142:4, L0769:4, H0555:4, L0750:4, H0543:4, H0341:3, L0534:3, H0486:3, L0649:3, L0666:3, H0658:3, L0749:3, L0758:3, H0624:2, S0040:2, L0415:2, H0261:2, H0549:2, H0550:2, H0618:2, H0052:2, S0150:2, L0805:2, L0807:2, L0657:2, L0790:2, H0539:2, S0380:2, L0748:2, L0747:2, L0731:2, L0759:2, S0434:2, H0685:1, S0114:1,

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	HRACD15	706332	273	
142	HRACJ35	877666	152	AR222:51, AR224:51, AR221:28, AR223:24, AR225:20, AR172:14, AR171:9, AR170:9, AR182:9, AR215:9, AR214:9, AR183:8, AR216:8, AR169:8, AR168:7, AR268:7, AR217:7, AR180:7, AR176:5, AR269:5, AR173:5, AR266:5, AR175:4, AR270:4, AR165:4, AR164:4, AR181:4, AR166:4, AR290:4, AR163:4, AR238:4, AR096:4, AR161:4, AR162:4, AR195:3, AR267:3, AR274:3, AR291:3, AR243:3, AR250:3, AR289:3, AR179:3, AR316:3, AR230:3, AR247:3, AR282:3, AR060:3, AR257:3, AR240:2, AR104:2, AR246:2, AR196:2, AR255:2, AR177:2, AR300:2, AR228:2, AR288:2, AR231:2, AR237:2, AR277:2, AR174:2, AR192:2, AR178:2, AR297:2, AR191:2, AR229:2, AR226:2, AR205:2, AR061:2, AR185:2, AR190:2, AR189:2, AR263:2, AR294:2, AR203:2, AR233:2, AR210:2, AR275:2, AR287:1, AR089:1, AR283:1, AR234:1, AR033:1, AR311:1, AR213:1, AR055:1, AR293:1, AR227:1, AR201:1, AR312:1, AR200:1, AR039:1, AR188:1, AR239:1, AR296:1, AR193:1 L0731:11, L0803:7, L0748:7, L0517:6, L0809:6, L0749:6, L0439:5, S0410:4, S0002:4, L0770:4, L0794:4, L0805:4, L3212:4, S0436:4, L3388:3, H0553:3, L0506:3, L0747:3, L0752:3, H0713:2, H0661:2, H0244:2, H0156:2, H0644:2, L0662:2, L0775:2, L0666:2, L0438:2, H0521:2, L0757:2, L0758:2, L0759:2, H0171:1, S0040:1, H0650:1, S0212:1, S0358:1, S0444:1, S0360:1, H0580:1, H0722:1, H0208:1, H0619:1, H0441:1, H0537:1, H0497:1, H0333:1, H0632:1, T0060:1, H0013:1, H0427:1, S0346:1, H0052:1, H0231:1, H0166:1, H0673:1, S0364:1, L0455:1, H0163:1, H0040:1, S0015:1, H0745:1, H0509:1, H0652:1, S0210:1, S0426:1, L0796:1, L0766:1, L0804:1, L0774:1, L0776:1, L0659:1, L0526:1, L0783:1, L0529:1, L0647:1, L0665:1, H0144:1, H0696:1, H0555:1, L0611:1, S0028:1, S0206:1, L0751:1, L0745:1, S0260:1, L0599:1, H0668:1, L0698:1 and S0460:1.
	HRACJ35	730504	274	
	HRACJ35	470546	275	
143	HRGBL78	910133	153	AR052:15, AR213:14, AR053:10, AR244:8, AR096:7, AR184:6, AR215:6, AR310:5, AR251:5, AR241:5, AR221:4, AR273:4, AR170:4, AR270:3, AR206:3, AR249:3, AR186:3, AR284:3, AR312:3, AR290:3, AR292:3, AR168:3, AR039:3, AR266:3, AR055:3, AR298:3, AR282:3, AR172:3, AR198:3, AR281:3, AR202:3, AR289:2, AR205:2, AR269:2, AR313:2, AR293:2, AR295:2, AR061:2, AR253:2, AR183:2, AR316:2, AR182:2, AR265:2, AR267:2, AR277:2, AR285:2, AR195:2, AR268:2, AR238:2, AR299:2, AR259:2, AR296:2, AR286:2, AR300:2, AR309:2, AR291:2, AR171:2, AR212:2, AR060:2, AR274:2, AR169:2, AR246:2, AR033:2, AR229:2, AR175:2, AR223:2, AR181:2, AR294:2, AR226:1, AR247:1, AR232:1, AR275:1, AR217:1, AR089:1, AR180:1, AR240:1, AR192:1, AR210:1, AR263:1, AR185:1, AR164:1, AR166:1, AR258:1, AR201:1, AR257:1, AR104:1, AR163:1, AR177:1, AR243:1 L0740:25, L0766:5, L0655:4, H0650:2, H0657:2, H0656:2, H0402:2, H0581:2, L0761:2, L0794:2, H0306:1, S0408:1, H0318:1, H0046:1, H0266:1, S0038:1, H0429:1, H0560:1, S0344:1, L0789:1, S0053:1, H0689:1, H0134:1, L0779:1, L0777:1 and H0445:1.

	HRGBL78	904040	276	
	HRGBL78	904621	277	
	HRGBL78	863802	278	
144	HROAJ39	1181699	154	AR055:8, AR060:6, AR218:6, AR300:5, AR316:4, AR089:4, AR240:4, AR282:3, AR185:3, AR104:3, AR299:3, AR313:3, AR096:3, AR283:3, AR039:2, AR219:2, AR277:2 H0316:1, L3905:1, L0565:1, L0438:1, H0521:1, L0439:1 and L0594:1.
	HROAJ39	1114849	279	
	HROAJ39	1027712	280	
145	HROBD68	827306	155	AR196:23, AR161:12, AR162:12, AR163:11, AR313:11, AR242:9, AR165:8, AR164:8, AR166:8, AR191:8, AR089:8, AR275:8, AR096:7, AR181:7, AR175:7, AR053:7, AR299:6, AR173:6, AR264:6, AR060:6, AR258:5, AR236:5, AR257:5, AR198:5, AR312:5, AR177:5, AR263:5, AR185:5, AR180:5, AR274:5, AR293:5, AR174:5, AR179:5, AR200:5, AR270:5, AR225:5, AR250:5, AR269:5, AR178:5, AR300:5, AR282:5, AR195:5, AR199:5, AR247:5, AR309:5, AR188:4, AR316:4, AR203:4, AR183:4, AR189:4, AR238:4, AR287:4, AR285:4, AR294:4, AR308:4, AR104:4, AR240:4, AR226:4, AR261:4, AR182:4, AR311:4, AR229:4, AR277:4, AR271:4, AR295:4, AR207:4, AR255:4, AR262:4, AR176:4, AR235:4, AR268:4, AR291:4, AR297:4, AR213:3, AR233:3, AR231:3, AR296:3, AR286:3, AR288:3, AR212:3, AR290:3, AR234:3, AR237:3, AR169:3, AR266:3, AR219:3, AR272:3, AR190:3, AR254:3, AR260:3, AR267:3, AR193:3, AR230:3, AR239:3, AR216:3, AR228:2, AR211:2, AR218:2, AR201:2, AR171:2, AR246:2, AR227:2, AR205:2, AR232:2, AR033:2, AR055:2, AR289:2, AR283:2, AR172:1, AR204:1, AR214:1, AR215:1, AR256:1, AR061:1, AR168:1, AR197:1, AR170:1, AR192:1 L0509:9, L0766:4, L0515:2, L0783:2, S0342:1, S0114:1, S0218:1, H0589:1, H0645:1, H0592:1, H0250:1, H0581:1, H0057:1, H0252:1, H0328:1, H0674:1, H0598:1, H0090:1, H0634:1, H0488:1, H0625:1, S0426:1, L0506:1, L0667:1, L0499:1, L0803:1, L0493:1, L0514:1, L0511:1, L0809:1, S0052:1, S0428:1, H0683:1, S0152:1, S0136:1, L0748:1, L0751:1, L0759:1, L0599:1 and H0543:1.
146	HSAWD74	460527	156	AR039:35, AR313:32, AR096:24, AR089:22, AR299:17, AR300:16, AR104:13, AR185:13, AR277:13, AR316:13, AR060:13, AR173:12, AR165:12, AR166:12, AR240:11, AR164:11, AR218:11, AR162:11, AR161:11, AR163:10, AR229:10, AR178:9, AR242:9, AR175:9, AR262:9, AR247:9, AR183:9, AR258:8, AR275:8, AR055:8, AR257:8, AR180:7, AR293:7, AR282:7, AR181:7, AR196:7, AR204:7, AR312:7, AR219:7, AR193:7, AR191:6, AR238:6, AR176:6, AR198:6, AR269:6, AR235:6, AR199:6, AR179:6, AR270:6, AR233:6, AR182:6, AR297:6, AR234:6, AR254:6, AR177:6, AR296:6, AR174:6, AR236:5, AR203:5, AR226:5, AR283:5, AR266:5, AR285:5, AR268:5, AR245:5, AR255:5, AR188:5, AR309:5, AR267:5, AR053:5, AR287:5, AR294:5, AR213:5, AR274:5, AR286:5, AR200:5, AR231:4, AR308:4, AR033:4, AR288:4, AR189:4, AR237:4, AR260:4, AR261:4, AR291:4, AR201:4, AR172:4, AR243:4, AR295:4, AR228:4, AR222:4, AR290:4, AR271:4, AR212:4, AR264:4, AR272:3, AR252:3, AR169:3, AR230:3, AR239:3, AR205:3, AR253:3, AR227:3, AR197:3, AR289:3, AR225:3, AR207:3, AR190:3, AR217:2, AR214:2, AR061:2, AR216:2, AR256:2, AR232:2, AR263:2, AR195:2, AR223:2, AR221:2, AR246:2, AR311:1, AR192:1, AR168:1, AR210:1, AR211:1 H0068:3, S0114:2, L0534:2, L0740:2, H0717:1, S0134:1, S0442:1, S0354:1, S0476:1, H0333:1, H0009:1, H0560:1, L5565:1 and H0576:1.
	HSAWD74	371416	281	
147	HSDEK49	1352253	157	AR290:45, AR268:37, AR240:23, AR267:22, AR269:16, AR270:14, AR234:10, AR055:10, AR238:10, AR184:9, AR292:8,

				AR291:8, AR179:8, AR183:8, AR284:7, AR177:7, AR182:6, AR060:6, AR299:5, AR295:5, AR285:5, AR244:5, AR293:5, AR175:5, AR096:4, AR185:3, AR229:3, AR249:3, AR296:3, AR316:3, AR231:3, AR298:3, AR289:3, AR104:3, AR237:3, AR286:2, AR089:2, AR226:2, AR204:2, AR266:2, AR282:2, AR294:2, AR227:2, AR313:2, AR247:2, AR300:2, AR233:2, AR248:2, AR259:2, AR275:2, AR256:2, AR039:1, AR033:1, AR277:1, AR263:1, AR061:1, AR258:1, AR232:1, AR271:1, AR283:1, AR310:1 H0031:7, L0439:7, L0754:7, L3388:6, L0731:6, S0002:5, H0580:4, H0575:3, H0309:3, L0438:3, H0555:3, L0758:3, S0360:2, L3649:2, H0553:2, S0344:2, S0426:2, L0775:2, S0330:2, L0747:2, L0779:2, S0260:2, L0599:2, L0603:2, H0739:1, H0170:1, S0116:1, S0354:1, S0444:1, L3645:1, H0270:1, S0280:1, H0590:1, H0581:1, H0251:1, H0014:1, H0355:1, H0030:1, H0644:1, H0674:1, H0090:1, H0063:1, S0142:1, L0770:1, L0769:1, L0651:1, L0776:1, L0659:1, L0519:1, L0664:1, H0682:1, L0749:1, L0752:1, S0031:1 and H0506:1.
	HSDEK49	625998	282	
148	HSDFJ26	834619	158	AR263:62, AR264:49, AR269:11, AR161:9, AR162:9, AR163:9, AR176:8, AR181:6, AR309:6, AR182:6, AR191:6, AR235:6, AR266:6, AR223:5, AR215:5, AR267:5, AR180:5, AR268:5, AR178:5, AR311:5, AR228:5, AR282:5, AR183:5, AR165:4, AR174:4, AR096:4, AR177:4, AR164:4, AR236:4, AR270:4, AR214:4, AR233:4, AR179:4, AR190:4, AR166:4, AR237:4, AR308:4, AR255:3, AR055:3, AR189:3, AR168:3, AR216:3, AR175:3, AR294:3, AR217:3, AR239:3, AR231:3, AR172:3, AR207:3, AR275:3, AR238:3, AR240:3, AR229:3, AR316:3, AR222:3, AR170:3, AR272:3, AR225:3, AR247:3, AR061:3, AR226:3, AR060:3, AR274:3, AR232:3, AR199:3, AR291:3, AR260:3, AR234:2, AR230:2, AR288:2, AR312:2, AR262:2, AR290:2, AR203:2, AR053:2, AR227:2, AR287:2, AR104:2, AR289:2, AR285:2, AR185:2, AR313:2, AR295:2, AR257:2, AR200:2, AR188:2, AR293:2, AR252:2, AR193:2, AR256:2, AR261:2, AR196:2, AR089:2, AR300:2, AR283:1, AR219:1, AR201:1, AR271:1, AR171:1, AR224:1, AR286:1, AR033:1, AR211:1, AR297:1, AR258:1, AR277:1 S0026:6, S0360:4, L0662:4, L0747:4, L0759:4, L0755:3, S0408:2, H0575:2, S0474:2, H0251:2, H0673:2, L0766:2, L0804:2, L0665:2, L0608:2, H0543:2, H0171:1, H0686:1, H0613:1, H0427:1, L0021:1, T0082:1, H0309:1, H0150:1, H0024:1, L0163:1, H0266:1, H0271:1, S0338:1, H0252:1, H0615:1, H0428:1, H0030:1, H0040:1, H0647:1, L0369:1, L0500:1, L0769:1, L0638:1, L0637:1, L0764:1, L0767:1, L0768:1, L0364:1, L0794:1, L0649:1, L0775:1, L0805:1, L0659:1, L0382:1, L0666:1, S0052:1, H0697:1, S0328:1, S0330:1, S0380:1, H0521:1, S0406:1, H0478:1, L0754:1, L0745:1, L0749:1, L0779:1, L0780:1, L0752:1, S0031:1, L0601:1, S0242:1 and H0542:1.
	HSDFJ26	836071	283	
149	HSDSB09	1301498	159	AR060:10, AR089:9, AR055:7, AR104:7, AR313:5, AR039:4, AR218:4, AR299:4, AR184:4, AR316:4, AR096:4, AR182:4, AR219:3, AR294:3, AR185:3, AR214:3, AR197:3, AR291:3, AR212:3, AR251:3, AR284:3, AR283:3, AR282:3, AR222:3, AR269:3, AR286:3, AR298:2, AR266:2, AR052:2, AR262:2, AR249:2, AR311:2, AR292:2, AR309:2, AR295:2, AR233:2, AR236:2, AR296:2, AR268:2, AR267:2, AR253:2, AR270:2, AR255:2, AR183:2, AR285:2, AR165:2, AR177:2, AR228:2, AR289:2, AR061:2, AR186:2, AR300:2, AR168:2, AR033:2, AR239:2, AR235:1, AR231:1, AR215:1, AR277:1, AR225:1, AR290:1, AR274:1, AR293:1, AR163:1, AR247:1, AR310:1, AR217:1, AR226:1, AR238:1, AR240:1, AR265:1, AR237:1, AR264:1, AR224:1, AR229:1, AR053:1, AR172:1, AR271:1 L0803:14, L0774:4, L0770:2, H0409:1, H0331:1 and H0555:1.
	HSDSB09	463645	284	
150	HSDSE75	545057	160	AR096:3, AR225:3, AR266:3, AR055:3, AR060:3, AR309:2, AR170:2, AR222:2, AR104:2, AR214:2, AR254:2, AR163:2, AR161:2, AR195:2, AR282:2, AR089:1, AR224:1, AR283:1, AR275:1, AR228:1, AR162:1, AR300:1, AR272:1, AR216:1,

				AR240:1, AR290:1, AR175:1, AR185:1, AR201:1, AR193:1, AR200:1, AR164:1, AR166:1, AR316:1, AR168:1, AR230:1, AR165:1, AR218:1 H0646:2, L0783:2, L0751:2, H0222:1, L3645:1, H0409:1, H0559:1, H0590:1, H0581:1, L0471:1, H0622:1, H0316:1, H0623:1, L0788:1, H0689:1, S0328:1, S0390:1, L0777:1, L0731:1 and L0462:1.
151	HSIDJ81	589447	161	AR313:41, AR039:35, AR096:26, AR173:25, AR299:21, AR258:20, AR180:20, AR185:19, AR089:18, AR262:18, AR161:18, AR162:18, AR179:18, AR269:17, AR240:17, AR300:17, AR175:17, AR163:17, AR257:17, AR165:17, AR191:17, AR229:17, AR196:16, AR164:16, AR247:16, AR316:16, AR166:15, AR218:15, AR183:15, AR277:15, AR178:14, AR181:14, AR199:14, AR182:13, AR234:13, AR270:13, AR293:13, AR236:13, AR174:13, AR233:12, AR200:12, AR238:12, AR268:11, AR189:11, AR260:11, AR285:11, AR060:11, AR219:11, AR297:11, AR294:10, AR104:10, AR203:10, AR226:10, AR188:10, AR287:10, AR255:10, AR296:10, AR176:10, AR177:10, AR267:10, AR282:9, AR230:9, AR275:9, AR290:8, AR264:8, AR231:8, AR261:8, AR237:8, AR242:8, AR190:8, AR192:8, AR288:7, AR274:7, AR286:7, AR055:7, AR291:7, AR228:7, AR239:7, AR235:7, AR033:7, AR295:6, AR227:6, AR263:6, AR266:6, AR197:5, AR211:5, AR308:5, AR053:5, AR256:5, AR250:5, AR232:4, AR210:4, AR272:4, AR213:4, AR283:4, AR271:4, AR289:4, AR312:4, AR252:4, AR193:4, AR212:3, AR223:3, AR246:3, AR311:3, AR225:3, AR061:3, AR169:3, AR205:3, AR198:3, AR170:2, AR215:2, AR201:2, AR207:2, AR243:2, AR309:2, AR224:2, AR171:2, AR168:2, AR217:2, AR216:2, AR172:2, AR195:1 H0036:1 and L0744:1.
152	HSKDA27	1352409	162	AR039:106, AR104:103, AR055:103, AR240:102, AR060:87, AR096:84, AR282:77, AR283:67, AR300:66, AR316:57, AR185:48, AR219:45, AR218:44, AR089:40, AR299:36, AR277:34, AR313:31 S0212:13, S0126:12, L0777:11, S0027:10, S0028:10, S0250:7, H0717:6, L0662:6, L0747:6, S0360:5, S0022:5, S0206:5, L0779:5, S0194:5, L0659:4, L0751:4, L0731:4, L0758:4, H0713:3, H0716:3, S0444:3, H0599:3, L0163:3, S0210:3, L0807:3, S0390:3, S0037:3, S3014:3, L0740:3, S0192:3, H0295:2, H0486:2, H0706:2, H0309:2, H0023:2, H0373:2, H0266:2, H0039:2, H0038:2, L0598:2, L3872:2, H0689:2, L0757:2, L0759:2, L0599:2, S0011:2, S0040:1, L2906:1, S0298:1, H0661:1, H0663:1, H0662:1, S0420:1, S0356:1, S0442:1, S0408:1, L2338:1, S0046:1, H0411:1, H0550:1, H0586:1, H0587:1, H0333:1, T0040:1, T0060:1, H0427:1, H0251:1, H0150:1, H0050:1, H0014:1, H0188:1, S0214:1, H0428:1, H0622:1, T0006:1, H0553:1, H0628:1, H0124:1, H0087:1, H0551:1, T0067:1, H0413:1, T0069:1, S0440:1, L0762:1, L0763:1, L0770:1, L0769:1, L0637:1, L0773:1, L0768:1, L0794:1, L0386:1, L0774:1, L0775:1, L0375:1, L0805:1, L0776:1, L0655:1, L0783:1, L0519:1, L0367:1, L0790:1, L0666:1, L0663:1, L2263:1, L0565:1, S0148:1, H0726:1, H0724:1, L0438:1, H0519:1, S0152:1, S0454:1, H0521:1, H0696:1, S3012:1, S0124:1, L0439:1, L0750:1, H0595:1, S0436:1, H0668:1, H0667:1, S0242:1, S0276:1 and L3603:1.
	HSKDA27	1074734	285	
	HSKDA27	872570	286	
153	HSKGN81	676075	163	AR252:303, AR263:240, AR211:227, AR272:220, AR210:215, AR216:184, AR253:180, AR250:170, AR264:169, AR242:163, AR172:160, AR245:160, AR274:155, AR254:148, AR247:147, AR313:142, AR165:141, AR053:139, AR225:136, AR195:131, AR215:129, AR221:129, AR308:124, AR197:123, AR214:123, AR212:122, AR170:119, AR166:118, AR224:118, AR213:117, AR171:115, AR205:113, AR312:113, AR162:109, AR217:108, AR309:106, AR199:106, AR271:105, AR164:100, AR198:93, AR168:92, AR169:92, AR188:92, AR207:91, AR275:91, AR173:91, AR256:90, AR291:89, AR240:89, AR163:86, AR296:82, AR246:82, AR222:81, AR311:78, AR290:78, AR223:77, AR282:76, AR161:75, AR297:75, AR289:75, AR196:74, AR261:73, AR243:71, AR178:70, AR295:70, AR260:69, AR175:67, AR183:66, AR200:65, AR174:63, AR285:63, AR201:62, AR096:61, AR299:60, AR179:59, AR189:59, AR288:56, AR180:56, AR033:55,

				AR258:55, AR266:55, AR300:55, AR267:54, AR181:51, AR192:51, AR262:51, AR293:50, AR268:50, AR255:49, AR204:48, AR270:47, AR316:47, AR039:46, AR190:43, AR238:43, AR235:43, AR182:42, AR089:41, AR229:40, AR236:39, AR269:39, AR277:38, AR232:38, AR061:38, AR219:37, AR218:37, AR257:37, AR286:37, AR185:37, AR203:36, AR287:35, AR283:35, AR191:35, AR193:34, AR230:34, AR231:33, AR177:32, AR239:30, AR176:30, AR237:29, AR234:27, AR104:27, AR226:26, AR294:25, AR060:24, AR055:18, AR233:17, AR227:14, AR228:10 H0556:14, L0666:5, L0438:5, L0439:5, L0751:5, H0266:4, L0665:4, L0777:4, H0161:3, H0645:3, H0599:3, H0594:3, L0763:3, H0436:3, L0747:3, L0758:3, L0759:3, H0423:3, H0265:2, H0141:2, S0045:2, S0476:2, H0575:2, H0421:2, T0041:2, H0529:2, L0770:2, L0771:2, L0657:2, L5623:2, L0664:2, H0670:2, H0518:2, S0044:2, L0749:2, L0757:2, L0588:2, L0599:2, H0585:1, L3643:1, H0717:1, H0716:1, H0740:1, H0583:1, S0116:1, H0341:1, H0254:1, H0255:1, H0306:1, H0402:1, S0360:1, S0408:1, S0046:1, S0132:1, H0619:1, H0549:1, H0550:1, S0222:1, H0614:1, H0392:1, H0455:1, H0613:1, H0592:1, H0586:1, H0587:1, S0005:1, H0497:1, H0492:1, H0486:1, H0250:1, T0071:1, H0581:1, H0052:1, H0309:1, H0545:1, H0050:1, L0471:1, H0024:1, L0183:1, H0267:1, H0687:1, H0286:1, H0328:1, L0483:1, L0053:1, H0628:1, H0169:1, H0674:1, S0366:1, H0038:1, H0634:1, H0264:1, H0488:1, H0268:1, H0100:1, T0042:1, H0494:1, S0014:1, H0625:1, H0509:1, H0641:1, S0002:1, L0637:1, L3905:1, L0646:1, L0773:1, L0662:1, L0768:1, L0652:1, L0776:1, L0659:1, L0783:1, S0374:1, H0783:1, H0593:1, S0126:1, H0659:1, H0658:1, H0648:1, H0672:1, S3012:1, S0028:1, L0754:1, L0750:1, L0731:1, S0260:1, S0436:1, L0596:1, L0581:1, S0242:1, S0194:1, H0543:1, S0446:1, H0506:1 and H0008:1.
	HSKGN81	409905	287	
154	HSNAD72	467397	164	AR170:5, AR169:4, AR180:4, AR313:4, AR221:3, AR178:3, AR223:3, AR245:3, AR192:3, AR235:2, AR204:2, AR182:2, AR299:2, AR216:2, AR291:2, AR274:2, AR171:2, AR214:2, AR217:2, AR193:2, AR266:1, AR308:1, AR293:1, AR257:1, AR247:1, AR232:1, AR225:1, AR283:1, AR210:1, AR282:1 H0163:2
155	HSNMC45	1352201	165	AR242:8, AR205:6, AR238:6, AR170:6, AR207:5, AR201:4, AR215:3, AR204:3, AR096:3, AR296:3, AR172:2, AR233:2, AR089:2, AR182:2, AR055:2, AR257:2, AR299:1, AR104:1, AR272:1, AR210:1, AR185:1, AR297:1 H0163:1
	HSNMC45	545060	288	
156	HSQFP66	460537	166	AR197:9, AR271:8, AR176:7, AR162:7, AR161:7, AR201:7, AR163:7, AR192:6, AR204:6, AR207:6, AR266:6, AR267:6, AR228:6, AR229:6, AR169:6, AR177:6, AR237:6, AR198:6, AR233:5, AR245:5, AR181:5, AR193:5, AR250:5, AR243:5, AR053:5, AR269:5, AR239:5, AR309:5, AR089:5, AR180:5, AR264:5, AR165:5, AR214:5, AR182:4, AR060:4, AR224:4, AR061:4, AR268:4, AR261:4, AR178:4, AR166:4, AR230:4, AR257:4, AR226:4, AR183:4, AR164:4, AR270:4, AR275:4, AR231:4, AR236:4, AR096:4, AR179:4, AR246:4, AR289:4, AR039:4, AR055:4, AR293:4, AR196:4, AR175:4, AR316:4, AR272:4, AR234:4, AR168:4, AR225:4, AR286:4, AR247:4, AR312:4, AR212:4, AR255:4, AR296:4, AR242:4, AR294:3, AR300:3, AR290:3, AR185:3, AR205:3, AR291:3, AR238:3, AR262:3, AR227:3, AR295:3, AR287:3, AR288:3, AR174:3, AR297:3, AR216:3, AR311:3, AR277:3, AR170:3, AR191:3, AR285:3, AR188:3, AR213:3, AR215:3, AR313:3, AR217:3, AR308:3, AR232:3, AR203:3, AR195:3, AR282:3, AR173:2, AR033:2, AR172:2, AR189:2, AR171:2, AR274:2, AR223:2, AR190:2, AR299:2, AR104:2, AR211:2, AR258:2, AR200:2, AR283:2, AR263:2, AR256:2, AR221:2, AR199:2, AR240:2, AR222:2, AR210:2, AR253:1, AR254:1, AR260:1, AR219:1, AR218:1 S0007:1, H0555:1 and S0026:1.
157	HSRFZ57	892171	167	AR225:4, AR309:4, AR060:4, AR192:3, AR235:3, AR162:3, AR055:3, AR161:3, AR163:3, AR215:3, AR275:3, AR169:3, AR254:3, AR217:3, AR233:2, AR170:2, AR177:2, AR181:2, AR236:2, AR255:2, AR228:2, AR180:2, AR289:2, AR237:2,

				AR243:2, AR239:2, AR166:2, AR285:2, AR266:2, AR272:2, AR287:2, AR222:2, AR274:2, AR176:2, AR061:2, AR271:2, AR223:2, AR247:2, AR214:1, AR224:1, AR240:1, AR172:1, AR213:1, AR283:1, AR262:1, AR295:1, AR033:1, AR089:1, AR174:1, AR229:1, AR216:1, AR234:1, AR238:1, AR231:1, AR316:1, AR218:1, AR300:1, AR293:1 S0022:4
158	HSUBW09	413246	168	AR186:66, AR202:60, AR259:59, AR206:59, AR292:58, AR061:56, AR052:56, AR283:51, AR227:49, AR251:49, AR244:48, AR249:47, AR281:45, AR310:44, AR280:44, AR033:43, AR055:42, AR194:42, AR192:41, AR241:41, AR273:40, AR300:40, AR314:38, AR185:38, AR248:38, AR315:37, AR104:36, AR232:36, AR299:35, AR233:34, AR229:34, AR237:34, AR275:34, AR184:33, AR060:32, AR265:31, AR039:31, AR177:29, AR198:28, AR053:28, AR294:28, AR282:27, AR243:26, AR256:26, AR309:25, AR313:25, AR231:25, AR246:25, AR295:25, AR298:24, AR089:24, AR219:24, AR096:24, AR274:24, AR312:23, AR204:23, AR293:22, AR284:22, AR267:21, AR205:21, AR316:21, AR271:21, AR247:20, AR226:20, AR238:19, AR213:19, AR175:19, AR234:18, AR218:17, AR253:16, AR289:16, AR277:14, AR258:14, AR179:13, AR266:12, AR286:12, AR263:12, AR285:12, AR296:12, AR183:11, AR291:11, AR270:10, AR240:9, AR182:9, AR268:8, AR269:8, AR290:8, AR163:5, AR287:4, AR176:3, AR250:3, AR215:3, AR225:2, AR201:2, AR172:2, AR224:2, AR221:2, AR272:2, AR264:2, AR214:1, AR165:1, AR195:1, AR193:1, AR257:1, AR216:1 L0766:5, L0749:3, S0134:2, L0770:2, L0794:2, L0809:2, L0790:2, H0556:1, H0735:1, L0622:1, H0457:1, H0561:1, L0662:1, L0804:1, L5622:1, H0436:1, L0779:1, L0731:1, L0758:1, H0136:1 and H0506:1.
159	HSVBU91	596868	169	AR215:6, AR207:5, AR162:4, AR161:4, AR163:4, AR309:4, AR271:4, AR266:4, AR165:4, AR176:4, AR164:4, AR272:3, AR039:3, AR192:3, AR213:3, AR253:3, AR166:3, AR264:3, AR089:3, AR282:3, AR204:3, AR235:3, AR205:3, AR313:3, AR053:3, AR201:2, AR224:2, AR178:2, AR275:2, AR181:2, AR267:2, AR182:2, AR269:2, AR277:2, AR104:2, AR286:2, AR246:2, AR287:2, AR289:2, AR033:2, AR243:2, AR237:2, AR230:2, AR223:2, AR268:2, AR293:2, AR180:2, AR060:2, AR175:2, AR198:2, AR229:2, AR177:2, AR270:2, AR233:2, AR183:2, AR228:2, AR261:2, AR239:2, AR316:2, AR285:2, AR179:2, AR232:1, AR231:1, AR312:1, AR061:1, AR288:1, AR257:1, AR096:1, AR291:1, AR225:1, AR226:1, AR294:1, AR295:1, AR185:1, AR311:1, AR227:1, AR234:1, AR174:1, AR203:1, AR297:1, AR173:1, AR191:1, AR247:1, AR308:1, AR238:1, AR216:1, AR255:1, AR170:1 H0309:1
160	HTAEE28	1018291	170	AR170:5, AR169:4, AR221:3, AR250:3, AR217:3, AR242:2, AR263:2, AR171:2, AR193:2, AR245:2, AR201:2, AR172:2, AR183:2, AR300:2, AR216:1, AR267:1, AR309:1, AR257:1, AR269:1, AR224:1, AR168:1, AR161:1, AR215:1, AR311:1 H0250:3, H0069:2, L0771:2, S0404:2, H0650:1, H0656:1, H0486:1, H0013:1, H0318:1, S0422:1, L0644:1, L0768:1, L0794:1, L0804:1, L0655:1, L0789:1, L0664:1, H0436:1 and L0758:1.
	HTAEE28	882919	289	
	HTAEE28	864120	290	
161	HTECC05	1352365	171	AR176:5, AR169:3, AR224:3, AR180:3, AR291:3, AR225:3, AR238:3, AR267:3, AR261:2, AR245:2, AR289:2, AR270:2, AR257:2, AR175:2, AR269:2, AR168:2, AR181:2, AR228:2, AR243:2, AR309:2, AR285:2, AR295:2, AR217:2, AR230:2, AR293:2, AR239:2, AR171:2, AR177:2, AR294:2, AR236:2, AR313:1, AR296:1, AR231:1, AR290:1, AR190:1, AR227:1, AR179:1, AR246:1, AR312:1, AR287:1, AR247:1, AR271:1, AR266:1, AR178:1, AR250:1, AR061:1, AR182:1, AR268:1, AR233:1, AR196:1, AR262:1, AR234:1, AR272:1, AR162:1, AR277:1, AR096:1 H0617:10, S0410:8, L0758:8, L0769:7, H0038:6, L0439:6, L0750:6, L0752:6, S0360:5, L0775:5, S0406:5, H0150:4, L0157:4, H0620:4, H0087:4, S0440:4, S0344:4, L0763:4, S0328:4, L0747:4, H0224:3, H0484:3, H0402:3, S0049:3, H0708:3, L0773:3, L0805:3, L0809:3, L0519:3, H0670:3,

				L0748:3, L0731:3, L0757:3, L0581:3, H0295:2, H0341:2, S0444:2, S0222:2, L0622:2, H0253:2, H0309:2, T0115:2, H0544:2, H0545:2, H0081:2, H0012:2, H0673:2, S0036:2, H0616:2, L0770:2, L0774:2, L0518:2, H0725:2, S0374:2, H0696:2, L0588:2, H0543:2, L0615:1, H0160:1, H0225:1, H0713:1, S6024:1, S0430:1, H0656:1, S0116:1, S0212:1, H0483:1, H0306:1, H0638:1, H0125:1, S0420:1, S0358:1, S0408:1, H0637:1, S0476:1, H0640:1, H0411:1, S0278:1, H0441:1, H0461:1, H0298:1, H0333:1, L0623:1, H0486:1, H0427:1, H0156:1, H0599:1, T0082:1, T0048:1, H0318:1, H0581:1, H0196:1, H0597:1, L0738:1, H0530:1, H0242:1, H0024:1, H0373:1, L0163:1, H0275:1, H0188:1, H0284:1, S0003:1, H0428:1, H0213:1, H0405:1, H0181:1, H0182:1, H0606:1, L0055:1, H0163:1, H0063:1, T0067:1, H0100:1, H0560:1, H0561:1, H0647:1, S0142:1, L0598:1, L3904:1, L0761:1, L0772:1, L0764:1, L0767:1, L0768:1, L0766:1, L0649:1, L0803:1, L0375:1, L0806:1, L0776:1, L0517:1, L0526:1, L0783:1, L0789:1, H0144:1, L0438:1, H0689:1, H0690:1, H0682:1, H0683:1, H0435:1, H0659:1, H0648:1, H0521:1, H0522:1, S3014:1, S0027:1, L0755:1, L0759:1, H0445:1, H0343:1, H0595:1, L0608:1, H0136:1, S0276:1, H0542:1, L0600:1 and H0352:1.
	HTECC05	877448	291	
	HTECC05	666743	292	
162	HTEEB42	206980	172	AR174:12, AR191:12, AR190:11, AR244:11, AR181:11, AR291:10, AR186:10, AR180:10, AR175:10, AR192:10, AR189:9, AR176:9, AR240:9, AR269:9, AR241:9, AR178:9, AR270:9, AR177:8, AR266:8, AR268:8, AR183:8, AR273:8, AR274:8, AR165:8, AR247:7, AR164:7, AR198:7, AR184:7, AR166:7, AR162:7, AR202:7, AR161:7, AR163:7, AR246:7, AR245:6, AR197:6, AR289:6, AR173:6, AR201:6, AR267:6, AR182:6, AR271:6, AR052:6, AR206:6, AR309:6, AR185:6, AR188:6, AR275:6, AR263:6, AR251:5, AR236:5, AR284:5, AR194:5, AR295:5, AR255:5, AR235:5, AR277:5, AR299:5, AR179:5, AR055:5, AR290:5, AR104:5, AR033:5, AR193:5, AR228:4, AR230:4, AR204:4, AR196:4, AR170:4, AR285:4, AR256:4, AR172:4, AR272:4, AR257:4, AR262:4, AR205:4, AR233:4, AR308:4, AR261:4, AR195:4, AR252:4, AR300:4, AR223:4, AR089:4, AR287:4, AR238:4, AR243:4, AR214:4, AR296:4, AR237:4, AR265:4, AR250:4, AR239:4, AR288:4, AR298:4, AR224:3, AR294:3, AR229:3, AR248:3, AR316:3, AR207:3, AR286:3, AR312:3, AR297:3, AR264:3, AR199:3, AR061:3, AR293:3, AR053:3, AR227:3, AR060:3, AR311:3, AR211:3, AR249:3, AR225:3, AR292:3, AR219:3, AR258:3, AR039:3, AR215:3, AR313:3, AR282:3, AR226:3, AR260:3, AR231:2, AR242:2, AR203:2, AR171:2, AR168:2, AR210:2, AR200:2, AR259:2, AR234:2, AR096:2, AR232:2, AR169:2, AR222:2, AR254:2, AR218:2, AR221:2, AR253:2, AR283:2, AR213:1, AR216:1, AR217:1, AR310:1 L0794:4, H0624:2, H0038:2, L0375:2, S0330:2, L0750:2, L0779:2, H0031:1, H0644:1, H0124:1, H0591:1, H0616:1, H0264:1, H0623:1, L0770:1, L0637:1, L0805:1, L0663:1, L0749:1, L0777:1, L0780:1 and L0599:1.
163	HTEFU65	543396	173	AR240:15, AR055:12, AR060:7, AR039:6, AR299:6, AR219:6, AR277:5, AR089:5, AR218:5, AR300:5, AR185:5, AR104:5, AR283:4, AR282:4, AR316:4, AR096:3, AR313:3 H0486:3, H0253:1, H0544:1, H0012:1, S0388:1, H0553:1, H0090:1, H0038:1, H0652:1, L0769:1, L0641:1, L0806:1, H0696:1, L0748:1, L0749:1, S0031:1 and S0196:1.
164	HTELP17	836072	174	AR263:33, AR223:32, AR214:31, AR309:30, AR224:29, AR264:29, AR283:27, AR308:27, AR222:27, AR169:25, AR235:25, AR172:25, AR277:24, AR212:23, AR053:23, AR168:23, AR213:22, AR171:22, AR316:21, AR221:21, AR311:21, AR261:21, AR217:20, AR089:20, AR170:20, AR055:19, AR219:19, AR282:19, AR165:19, AR312:19, AR162:19, AR225:19, AR216:19, AR161:18, AR164:18, AR176:18, AR218:18, AR033:18, AR295:18, AR163:18, AR207:18, AR104:18, AR096:17, AR236:17, AR166:17, AR215:16, AR299:16, AR177:16, AR240:16, AR060:16, AR196:15, AR288:15, AR266:15, AR300:15, AR269:15,

				AR039:15, AR200:15, AR181:15, AR313:15, AR291:14, AR178:14, AR293:14, AR185:14, AR272:14, AR286:14, AR253:13, AR210:13, AR294:13, AR270:13, AR296:13, AR285:13, AR227:13, AR239:13, AR297:13, AR233:12, AR174:12, AR245:12, AR183:12, AR252:12, AR192:12, AR230:12, AR226:12, AR287:12, AR175:12, AR257:12, AR195:12, AR258:12, AR274:12, AR229:11, AR289:11, AR237:11, AR179:11, AR267:11, AR255:11, AR247:11, AR061:11, AR262:11, AR290:11, AR231:11, AR191:11, AR275:11, AR268:11, AR180:10, AR182:10, AR199:10, AR234:10, AR204:10, AR205:10, AR173:10, AR188:10, AR228:10, AR232:10, AR238:9, AR198:9, AR190:9, AR197:9, AR203:9, AR256:9, AR189:8, AR254:8, AR250:8, AR246:7, AR211:7, AR193:7, AR260:7, AR243:7, AR201:7, AR271:6, AR242:5 L0758:3, S0408:2, H0031:2, H0038:2, L0766:2, H0521:2, L0748:2, H0341:1, L3659:1, S0476:1, H0581:1, S0051:1, H0266:1, H0111:1, H0616:1, L0794:1, L0805:1, L0787:1, L0779:1, L0759:1, L0593:1, H0542:1 and H0543:1.
165	HTELS08	847090	175	AR235:6, AR215:6, AR242:5, AR162:4, AR161:4, AR192:4, AR165:4, AR053:4, AR163:4, AR269:4, AR164:4, AR291:4, AR288:4, AR166:4, AR176:4, AR221:4, AR257:4, AR282:3, AR236:3, AR217:3, AR264:3, AR261:3, AR196:3, AR178:3, AR270:3, AR177:3, AR272:3, AR181:3, AR255:3, AR297:3, AR294:3, AR172:3, AR182:3, AR295:3, AR296:3, AR055:3, AR060:3, AR285:3, AR179:3, AR240:3, AR191:3, AR287:3, AR216:3, AR293:3, AR175:3, AR183:3, AR225:3, AR313:3, AR199:3, AR180:3, AR238:3, AR233:3, AR195:3, AR223:2, AR239:2, AR228:2, AR173:2, AR168:2, AR311:2, AR262:2, AR290:2, AR263:2, AR237:2, AR268:2, AR188:2, AR266:2, AR033:2, AR229:2, AR247:2, AR207:2, AR277:2, AR286:2, AR174:2, AR300:2, AR267:2, AR193:2, AR250:2, AR230:2, AR258:2, AR189:2, AR246:2, AR289:2, AR096:2, AR231:2, AR283:2, AR185:2, AR089:2, AR222:2, AR275:2, AR308:2, AR201:2, AR260:2, AR190:2, AR316:2, AR312:2, AR061:2, AR226:2, AR243:2, AR299:2, AR104:2, AR171:1, AR200:1, AR219:1, AR309:1, AR227:1, AR203:1, AR256:1, AR039:1, AR234:1, AR169:1, AR232:1 H0616:2, L0758:2 and H0038:1.
166	HTLEP53	634852	176	AR173:20, AR262:20, AR313:19, AR196:16, AR161:16, AR162:15, AR175:15, AR163:15, AR258:15, AR165:15, AR164:14, AR166:14, AR178:13, AR257:13, AR300:13, AR179:13, AR181:12, AR233:12, AR229:12, AR174:12, AR183:12, AR247:12, AR240:11, AR234:11, AR177:11, AR191:11, AR200:10, AR236:10, AR293:10, AR242:10, AR199:10, AR269:10, AR182:10, AR180:10, AR260:9, AR255:9, AR275:8, AR238:8, AR264:8, AR228:8, AR270:8, AR261:8, AR188:8, AR297:8, AR231:8, AR185:8, AR226:8, AR294:8, AR296:8, AR176:8, AR312:8, AR287:8, AR203:7, AR219:7, AR268:7, AR290:7, AR230:7, AR033:7, AR267:7, AR274:7, AR096:7, AR237:7, AR213:7, AR189:7, AR285:6, AR286:6, AR288:6, AR197:6, AR295:6, AR053:6, AR212:6, AR308:6, AR291:6, AR204:6, AR218:6, AR266:6, AR309:6, AR198:6, AR089:5, AR235:5, AR282:5, AR193:5, AR170:5, AR299:5, AR263:5, AR239:5, AR256:5, AR210:5, AR190:5, AR277:5, AR289:5, AR316:5, AR169:4, AR217:4, AR192:4, AR060:4, AR201:4, AR223:4, AR227:4, AR245:4, AR171:4, AR252:4, AR243:4, AR221:4, AR232:4, AR211:4, AR061:4, AR272:4, AR271:3, AR311:3, AR195:3, AR205:3, AR039:3, AR172:3, AR250:3, AR214:2, AR207:2, AR055:2, AR168:2, AR222:2, AR283:2, AR224:2, AR104:2, AR215:2, AR216:1, AR225:1 H0253:1
167	HTPCS72	854941	177	AR219:14, AR218:13, AR104:11, AR240:9, AR060:8, AR055:7, AR299:7, AR096:7, AR316:7, AR185:6, AR313:6, AR089:6, AR300:6, AR039:5, AR283:4, AR282:4, AR277:2 L0438:6, L0439:5, H0661:3, L0776:3, H0556:2, H0100:2, L0598:2, L0764:2, L0766:2, H0672:2, L0777:2, L0731:2, H0170:1, H0171:1, H0265:1, H0140:1, S0114:1, H0657:1, H0656:1, H0638:1, S0418:1, S0408:1, H0730:1, H0741:1, S0046:1, H0411:1, S0278:1, H0550:1, S0222:1, T0104:1, H0600:1, S0280:1, S0474:1, H0007:1, T0110:1, H0046:1, H0457:1, H0150:1, H0566:1, H0620:1, H0057:1, H0039:1, H0030:1, L0055:1, H0090:1, H0413:1, H0623:1, H0059:1, H0647:1, H0529:1, L0770:1, L0646:1, L0645:1, L0521:1, L0794:1, L0650:1, L0659:1,

				L5623:1, L0789:1, L0666:1, L0663:1, L0664:1, H0144:1, H0547:1, S0152:1, L0740:1, L0747:1, L0750:1, L0756:1, L0779:1, L0757:1, L0758:1, L0595:1 and H0422:1.
	HTPCS72	566683	293	
168	HTPIH83	919916	178	AR176:5, AR180:5, AR266:5, AR182:5, AR223:4, AR267:4, AR183:4, AR233:4, AR269:4, AR181:4, AR228:4, AR236:4, AR245:4, AR224:4, AR169:3, AR225:3, AR238:3, AR231:3, AR168:3, AR257:3, AR229:3, AR161:3, AR162:3, AR177:3, AR293:3, AR237:3, AR221:3, AR289:3, AR163:3, AR268:3, AR239:3, AR215:3, AR261:3, AR288:3, AR170:3, AR175:3, AR226:3, AR174:3, AR199:3, AR290:3, AR179:2, AR191:2, AR255:2, AR264:2, AR234:2, AR061:2, AR217:2, AR240:2, AR282:2, AR216:2, AR294:2, AR060:2, AR196:2, AR287:2, AR172:2, AR173:2, AR178:2, AR285:2, AR295:2, AR200:2, AR291:2, AR222:2, AR190:2, AR247:2, AR189:2, AR309:2, AR203:2, AR188:2, AR300:2, AR230:2, AR311:2, AR296:2, AR262:2, AR171:2, AR275:2, AR235:1, AR232:1, AR227:1, AR258:1, AR286:1, AR033:1, AR297:1, AR039:1, AR256:1, AR316:1, AR313:1, AR089:1, AR185:1, AR277:1 H0622:7, S0360:3, L0809:3, L0804:2, L0774:2, L0775:2, L0748:2, H0484:1, H0014:1, S0440:1, L0646:1, L0643:1, L0374:1, L0764:1, L0771:1, L0773:1, L0662:1, L0803:1 and L0788:1.
	HTPIH83	895024	294	
	HTPIH83	898088	295	
169	HTSEW17	460579	179	AR170:7, AR161:7, AR162:7, AR163:7, AR182:7, AR225:6, AR176:6, AR282:5, AR228:5, AR223:5, AR266:5, AR180:5, AR224:5, AR178:5, AR269:5, AR181:5, AR261:5, AR309:5, AR233:5, AR250:5, AR191:5, AR216:4, AR257:4, AR231:4, AR267:4, AR236:4, AR268:4, AR274:4, AR229:4, AR270:4, AR214:4, AR179:4, AR239:4, AR165:4, AR288:4, AR247:4, AR263:4, AR089:4, AR255:4, AR237:4, AR061:4, AR164:4, AR287:3, AR275:3, AR240:3, AR177:3, AR096:3, AR264:3, AR174:3, AR166:3, AR183:3, AR234:3, AR293:3, AR291:3, AR295:3, AR173:3, AR300:3, AR168:3, AR200:3, AR299:3, AR190:3, AR221:3, AR196:3, AR296:3, AR290:3, AR316:3, AR294:3, AR262:3, AR175:3, AR297:3, AR185:3, AR238:3, AR313:3, AR060:3, AR230:3, AR055:3, AR039:3, AR283:3, AR286:3, AR227:3, AR260:2, AR172:2, AR285:2, AR053:2, AR308:2, AR217:2, AR311:2, AR188:2, AR277:2, AR203:2, AR226:2, AR272:2, AR232:2, AR192:2, AR222:2, AR189:2, AR201:2, AR213:2, AR312:2, AR258:2, AR193:2, AR289:2, AR171:2, AR199:2, AR256:1, AR219:1, AR212:1, AR215:1, AR211:1, AR033:1, AR218:1 H0087:1, S0002:1, L0769:1, L0789:1, H0683:1, H0670:1, L0748:1, L0749:1, L0752:1 and L0758:1.
170	HTTBI76	637725	180	AR252:4, AR214:4, AR309:3, AR169:3, AR297:3, AR193:3, AR250:3, AR271:3, AR291:3, AR161:3, AR272:2, AR033:2, AR294:2, AR217:2, AR221:2, AR223:2, AR312:2, AR168:2, AR163:2, AR261:2, AR181:2, AR210:1, AR197:1, AR225:1, AR205:1, AR267:1, AR270:1, AR165:1, AR222:1, AR216:1, AR170:1, AR295:1, AR166:1, AR213:1 L0803:4, L0731:4, L0774:3, S0380:3, S0028:3, L0758:3, H0486:2, S0003:2, H0040:2, S0344:2, L0766:2, L0775:2, H0547:2, L0748:2, L0756:2, L0777:2, L0780:2, L0753:2, S0011:2, H0716:1, H0638:1, L0617:1, S0358:1, H0411:1, S0280:1, H0318:1, H0355:1, H0674:1, H0212:1, H0135:1, H0038:1, H0132:1, S0142:1, S0002:1, H0529:1, L0804:1, L0632:1, L0666:1, H0682:1, H0684:1, H0525:1, S0044:1, S0406:1, H0555:1, L0747:1, L0750:1, L0752:1, L0755:1, L0604:1 and S0026:1.
171	HTTBS64	1008159	181	AR282:4, AR252:4, AR269:3, AR171:3, AR170:3, AR264:2, AR176:2, AR291:2, AR311:2, AR225:2, AR277:2, AR168:2, AR270:2, AR172:2, AR262:1, AR271:1, AR055:1, AR272:1, AR299:1, AR257:1, AR313:1 H0040:1
	HTTBS64	863187	296	

	HTTBS64	754125	297	
172	HTXJM03	603918	182	AR313:13, AR252:10, AR282:8, AR312:7, AR176:7, AR096:7, AR269:6, AR254:6, AR201:6, AR196:6, AR245:6, AR250:6, AR270:6, AR197:6, AR053:6, AR161:6, AR162:6, AR180:6, AR089:6, AR163:6, AR169:6, AR191:5, AR170:5, AR240:5, AR165:5, AR178:5, AR183:5, AR290:5, AR164:5, AR166:5, AR300:5, AR257:5, AR039:5, AR264:5, AR229:5, AR203:5, AR266:5, AR268:5, AR267:5, AR255:5, AR181:5, AR236:5, AR297:5, AR233:4, AR296:4, AR309:4, AR182:4, AR193:4, AR228:4, AR179:4, AR175:4, AR188:4, AR247:4, AR316:4, AR173:4, AR177:4, AR293:4, AR271:4, AR231:4, AR213:4, AR060:4, AR225:4, AR308:4, AR212:4, AR243:4, AR285:4, AR200:4, AR199:4, AR192:4, AR287:4, AR189:4, AR294:4, AR286:4, AR238:4, AR299:3, AR291:3, AR295:3, AR239:3, AR261:3, AR237:3, AR263:3, AR198:3, AR283:3, AR172:3, AR185:3, AR216:3, AR204:3, AR288:3, AR311:3, AR234:3, AR205:3, AR262:3, AR258:3, AR289:3, AR055:3, AR277:3, AR224:3, AR207:3, AR230:3, AR168:3, AR226:3, AR223:3, AR061:3, AR190:2, AR174:2, AR218:2, AR227:2, AR195:2, AR256:2, AR274:2, AR260:2, AR217:2, AR235:2, AR033:2, AR246:2, AR275:2, AR171:2, AR219:2, AR104:2, AR232:1, AR253:1, AR211:1, AR210:1, AR242:1 L0766:5, H0313:3, H0624:1, H0265:1, H0556:1, S0116:1, H0329:1, H0486:1, H0156:1, H0590:1, H0009:1, S0250:1, H0169:1, S0450:1, S0002:1, L0769:1, L0793:1, L0532:1, L0750:1, L0777:1 and S0424:1.
173	HTXON32	838288	183	AR195:107, AR197:91, AR172:81, AR246:78, AR295:74, AR272:72, AR258:71, AR196:67, AR224:67, AR235:67, AR171:66, AR193:66, AR291:63, AR297:59, AR223:58, AR168:57, AR200:56, AR263:55, AR222:54, AR170:53, AR261:53, AR245:52, AR236:52, AR169:52, AR311:49, AR256:49, AR225:49, AR188:48, AR173:48, AR285:48, AR288:47, AR221:46, AR260:46, AR198:46, AR313:46, AR174:45, AR201:45, AR271:45, AR191:44, AR175:44, AR217:44, AR286:44, AR287:43, AR309:43, AR270:43, AR264:42, AR211:42, AR274:42, AR308:41, AR199:41, AR181:40, AR294:40, AR214:39, AR262:39, AR216:39, AR243:39, AR189:39, AR275:38, AR177:38, AR215:38, AR033:38, AR255:37, AR296:37, AR210:36, AR190:36, AR257:36, AR289:35, AR213:35, AR282:34, AR240:34, AR218:34, AR163:32, AR247:32, AR176:31, AR180:30, AR312:30, AR254:30, AR212:30, AR166:29, AR300:29, AR162:29, AR293:29, AR203:29, AR183:29, AR219:28, AR161:28, AR192:28, AR242:28, AR165:27, AR250:27, AR269:27, AR185:27, AR164:26, AR039:25, AR104:25, AR266:24, AR290:24, AR316:24, AR179:23, AR182:23, AR178:23, AR096:22, AR238:21, AR053:21, AR205:20, AR268:20, AR089:20, AR207:19, AR267:19, AR299:19, AR204:19, AR229:18, AR234:18, AR226:17, AR277:17, AR231:17, AR253:16, AR237:15, AR232:14, AR230:14, AR233:14, AR060:13, AR283:11, AR239:10, AR055:9, AR061:9, AR228:9, AR252:8, AR227:6 H0556:1
174	HUFCJ30	638402	184	AR277:9, AR207:8, AR215:7, AR192:7, AR170:6, AR223:6, AR282:6, AR235:6, AR216:6, AR225:6, AR165:6, AR169:6, AR171:6, AR164:5, AR245:5, AR168:5, AR166:5, AR198:5, AR222:5, AR089:5, AR242:5, AR183:5, AR195:5, AR221:5, AR193:4, AR224:4, AR214:4, AR313:4, AR252:4, AR172:4, AR243:4, AR236:4, AR201:4, AR299:4, AR295:4, AR246:4, AR238:4, AR264:4, AR176:4, AR161:4, AR240:4, AR162:4, AR309:4, AR204:4, AR263:4, AR163:4, AR261:4, AR217:4, AR297:4, AR316:3, AR285:3, AR182:3, AR269:3, AR270:3, AR205:3, AR308:3, AR197:3, AR060:3, AR311:3, AR230:3, AR055:3, AR173:3, AR196:3, AR250:3, AR288:3, AR272:3, AR213:3, AR234:3, AR181:3, AR312:3, AR283:3, AR199:3, AR180:3, AR033:3, AR266:3, AR175:3, AR254:3, AR177:3, AR262:3, AR296:3, AR300:3, AR268:3, AR290:3, AR231:3, AR287:3, AR247:3, AR294:3, AR191:3, AR275:3, AR291:2, AR237:2, AR228:2, AR179:2, AR174:2, AR096:2, AR289:2, AR178:2, AR233:2, AR229:2, AR286:2, AR255:2, AR226:2, AR185:2, AR293:2, AR200:2, AR188:2, AR189:2, AR227:2, AR257:2, AR212:2, AR203:2, AR239:2, AR104:2, AR053:2, AR061:2, AR258:2, AR039:2, AR232:2, AR271:2, AR218:2,

				AR219:2, AR260:2, AR190:2, AR267:2, AR210:1 L0777:7, L0751:3, L0766:2, L0438:2, L0779:2, H0352:2, H0351:1, S0222:1, H0333:1, H0687:1, H0646:1, L0770:1, L0642:1, L0662:1, L0803:1, L0375:1, L0805:1, L0653:1, L0659:1, L0790:1, L0663:1, L0664:1, L0665:1 and H0506:1.
175	HUVEB53	571200	185	AR053:3, AR171:3, AR224:3, AR180:2, AR168:2, AR207:2, AR165:2, AR282:2, AR217:2, AR299:2, AR234:1, AR277:1, AR296:1, AR295:1, AR164:1, AR261:1, AR166:1, AR204:1, AR225:1, AR257:1, AR283:1, AR269:1, AR183:1 H0171:3, L0754:3, H0431:2, H0196:2, H0546:2, H0623:2, H0539:2, H0696:2, L0744:2, L0748:2, L0749:2, L0758:2, L0759:2, S0398:2, H0624:1, T0002:1, S0040:1, H0341:1, S0360:1, H0580:1, H0587:1, H0574:1, H0486:1, H0036:1, S0665:1, H0123:1, H0014:1, S6028:1, S0214:1, H0553:1, H0032:1, L0455:1, H0598:1, H0038:1, H0616:1, H0056:1, S0386:1, S0112:1, T0042:1, S0344:1, S0422:1, S0002:1, L0775:1, L0806:1, L0805:1, L0776:1, S0152:1, H0704:1, H0555:1, H0436:1, L0439:1, L0751:1, L0752:1, L0731:1, L0588:1, L0592:1, S0026:1, H0543:1 and H0423:1.
176	HWAAD63	838626	186	AR196:17, AR173:14, AR161:14, AR162:14, AR241:14, AR163:14, AR165:13, AR313:12, AR166:12, AR164:12, AR262:12, AR264:11, AR236:11, AR199:10, AR191:10, AR174:9, AR178:9, AR257:9, AR235:9, AR180:9, AR263:8, AR203:8, AR181:8, AR200:8, AR229:8, AR274:7, AR189:7, AR275:7, AR311:7, AR240:7, AR247:7, AR297:7, AR312:7, AR175:7, AR308:7, AR212:7, AR261:7, AR169:7, AR265:7, AR188:7, AR234:6, AR177:6, AR221:6, AR194:6, AR287:6, AR242:6, AR258:6, AR207:6, AR230:6, AR255:6, AR176:6, AR293:6, AR168:6, AR271:6, AR224:6, AR179:6, AR270:6, AR185:6, AR192:6, AR233:5, AR198:5, AR300:5, AR096:5, AR214:5, AR216:5, AR183:5, AR238:5, AR272:5, AR269:5, AR039:5, AR226:5, AR223:5, AR299:5, AR296:5, AR215:5, AR285:5, AR260:5, AR089:5, AR288:5, AR182:4, AR204:4, AR239:4, AR228:4, AR222:4, AR213:4, AR309:4, AR231:4, AR060:4, AR033:4, AR210:4, AR252:4, AR273:4, AR286:4, AR053:4, AR268:4, AR294:4, AR237:4, AR193:4, AR172:4, AR243:4, AR218:4, AR267:4, AR277:4, AR310:4, AR104:3, AR295:3, AR291:3, AR190:3, AR225:3, AR282:3, AR316:3, AR227:3, AR290:3, AR171:3, AR217:3, AR186:3, AR211:3, AR266:3, AR195:3, AR219:3, AR249:3, AR292:3, AR052:3, AR201:3, AR206:2, AR245:2, AR314:2, AR232:2, AR202:2, AR298:2, AR289:2, AR315:2, AR256:2, AR244:2, AR259:2, AR205:2, AR246:2, AR061:1, AR184:1, AR284:1, AR280:1, AR283:1, AR055:1 H0441:1, H0581:1 and H0604:1.
	HWAAD63	833089	298	
	HWAAD63	793875	299	
177	HWADJ89	799506	187	AR252:29, AR250:29, AR253:21, AR254:10, AR282:6, AR215:6, AR165:5, AR164:5, AR166:5, AR089:5, AR161:5, AR246:5, AR162:5, AR271:5, AR240:5, AR053:5, AR163:5, AR263:4, AR243:4, AR274:4, AR195:4, AR205:4, AR313:4, AR096:4, AR299:4, AR180:4, AR213:4, AR193:4, AR214:4, AR169:4, AR300:4, AR311:4, AR264:4, AR192:4, AR173:4, AR207:4, AR312:3, AR285:3, AR171:3, AR309:3, AR060:3, AR275:3, AR308:3, AR196:3, AR272:3, AR316:3, AR269:3, AR257:3, AR261:3, AR170:3, AR270:3, AR183:3, AR242:3, AR245:3, AR296:3, AR199:3, AR287:3, AR295:3, AR175:3, AR033:3, AR172:3, AR222:2, AR188:2, AR039:2, AR185:2, AR290:2, AR286:2, AR247:2, AR238:2, AR191:2, AR297:2, AR178:2, AR268:2, AR291:2, AR262:2, AR200:2, AR235:2, AR104:2, AR283:2, AR212:2, AR210:2, AR288:2, AR203:2, AR201:2, AR174:2, AR277:2, AR182:2, AR197:2, AR189:2, AR255:2, AR294:2, AR229:2, AR230:2, AR293:2, AR258:2, AR216:2, AR236:2, AR224:2, AR181:2, AR190:2, AR239:2, AR228:2, AR227:2, AR233:2, AR234:1, AR177:1, AR231:1, AR179:1, AR061:1, AR266:1, AR055:1, AR226:1, AR221:1, AR289:1, AR232:1 H0581:1
178	HWBFX31	799427	188	AR171:3, AR309:2, AR271:2, AR282:2, AR225:2, AR205:2, AR267:2, AR213:2, AR257:2, AR236:2, AR053:1, AR266:1,

				AR179:1, AR199:1, AR270:1, AR214:1, AR181:1, AR240:1, AR247:1, AR277:1 L0659:5, L0794:4, L0809:4, L0777:4, H0424:3, L0766:3, L0745:3, H0265:2, H0656:2, H0254:2, H0662:2, S0376:2, H0457:2, H0024:2, L0768:2, H0670:2, H0555:2, L0751:2, L0780:2, H0556:1, H0218:1, H0224:1, H0638:1, S0360:1, H0675:1, S0408:1, H0580:1, H0586:1, H0575:1, H0545:1, H0050:1, H0188:1, H0252:1, H0039:1, H0617:1, H0316:1, H0063:1, H0087:1, H0264:1, H0272:1, H0652:1, S0002:1, S0426:1, L0763:1, L0770:1, L0761:1, L0800:1, L0773:1, L0648:1, L0662:1, L0774:1, L0784:1, L0776:1, L0647:1, L0790:1, L0666:1, L0664:1, L0665:1, L0438:1, H0521:1, H0522:1, L0749:1, L0750:1, L0752:1, L0757:1, L0759:1, L0596:1, H0422:1, S0458:1 and H0677:1.

Table 1C summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID:), contig sequences (contig identifier (Contig ID:) contig nucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier, "Clone ID:", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO:X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID:" for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO:A" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO:B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon From-To", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention that are also exemplary members of polynucleotide sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

Table 1C

cDNA Clone ID	SEQ ID NO:X	CONTIG ID:	BAC ID: A	SEQ ID NO:B	EXON From-To
HAUAI83	22	639009	AC010422	589	1-326 1552-2084 2162-2261 2300-2427 4485-5868 5948-6362 7914-8017 8569-8681 8765-8875 8968-9037 9284-9499 9742-9910 10837-11187 11271-11321 11554-11707 11783-12766 12866-13225 13256-13827 14284-14367 14890-15090
HAUAI83	22	639009	AC018761	590	1-326 1176-1284 1552-2084 2162-2261 2300-2426 4485-5868

					5948-6362 8569-8681 8765-8875 8968-9037 9284-9499 9742-9910 10317-10501 10837-11187 11271-11321 11554-11707 11783-12766 12866-13225 13256-13827 14284-14367 14890-15090
HAUAI83	22	639009	AC010422	591	1-315 2004-2289 2650-2741 3554-3830
HAUAI83	22	639009	AC010422	592	1-202 938-1047 1219-1395 1758-1956 2907-3429 3792-3935 5366-5485 6391-6688 6899-7269 7890-8316 8400-8524 8607-8682 8824-8999 9190-9302 9691-9796 10106-10177 10571-11051 11164-11490 12565-12696 13364-13501 13964-14592 14740-15540 15610-15798 15947-16642 16717-16832 16968-17408 17521-17612 18331-18579 19120-19303 19358-19514 19599-19702 20003-20245
HAUAI83	22	639009	AC018761	593	1-202 938-1047 1219-1395 1758-1956

					2907-3429 3792-3935 5366-5485 6391-6688 6899-7269 7591-7711 7890-8316 8400-8524 8607-8682 8749-9073 9190-9302 9691-9796
HAUAI83	22	639009	AC018761	594	1-82 128-293 1178-1447 1986-2278 2457-2711 3543-3844
HBINS58	26	1352386	AL096774	595	1-1023 2010-2239 2581-2962 3153-3223 3324-3493 3973-4126
HBINS58	26	1352386	AL096774	596	1-341
HBINS58	26	1352386	AL096774	597	1-142
HCE3G69	29	728432	AC068946	598	1-108 1186-1324 1746-1835 2138-2284 2448-2545 2718-2861 3091-5889
HCE3G69	29	728432	AC068946	599	1-191
HCE3G69	29	728432	AC068946	600	1-686
HCEFB80	31	1143407	AL022327	601	1-2271 3506-3658 4643-4810 9039-9164 9382-9509 10587-10720 11135-11195 11265-11716 14644-15466 17451-17526 18012-18114 20530-20632 20957-21009 23696-23785 25338-25575 25969-26166
HCNDR47	34	1016919	AL122003	602	1-236 531-696 787-817

					863-4508 5158-5744 6949-7029
HCNDR47	34	1016919	AL122003	603	1-888 1304-2003 2830-3284 3719-4571 4618-5268 6131-6557 8947-9033 9058-9726 14176-14480 18456-18915 18960-19871 22365-22454 23082-23248 28058-28215
HDPGT01	44	771583	AC020978	604	1-180 2776-2899 3916-4077 4296-4335 4436-4632 4895-5181 8153-8246 9547-9666 9907-10007 10370-10618 10788-11046 11926-13423 13465-13494 13764-15689
HDPGT01	44	771583	AC020978	605	1-384
HDPSB18	50	1043263	AL355512	606	1-2572 3049-3871
HDPSB18	50	1043263	AC006176	607	1-2571 3048-3872
HDPSB18	50	1043263	AL355512	608	1-280
HDPXY01	55	879048	AL354000	609	1-1319 4848-4975 5229-5600 6561-6654
HDPXY01	55	879048	AL035362	610	1-1316 4844-4971 5225-5596 6557-6650
HDPXY01	55	879048	AL354000	611	1-460
HDPXY01	55	879048	AL354000	612	1-400
HDPXY01	55	879048	AL035362	613	1-400
HDPXY01	55	879048	AL035362	614	1-460
HHGCG53	80	340818	AC024037	615	1-518
HHGCM76	81	662329	AC003665	616	1-70 304-609 900-1090 1240-1835

					2272-2490 2581-3598
HHGCM76	81	662329	AC003665	617	1-580 851-995 1224-1296 1314-1663 1930-1975 2724-2905 2968-3098 3283-3328 5121-5230 5331-5689
HJACG30	84	895505	AC018512	618	1-776
HJACG30	84	895505	AC022305	619	1-878
HJACG30	84	895505	AC002518	620	1-150
HLTIP94	105	1087335	AC007431	621	1-1299
HLTIP94	105	1087335	AC007431	622	1-330
HMSDL37	115	973996	AC012086	623	1-3328
HMSDL37	115	973996	AC018811	624	1-3051
HMSDL37	115	973996	AC018494	625	1-3029
HMSDL37	115	973996	AC012086	626	1-224
HMSDL37	115	973996	AC012086	627	1-468
HMSDL37	115	973996	AC018811	628	1-222
HMSDL37	115	973996	AC018811	629	1-468
HMSDL37	115	973996	AC018494	630	1-224
HMSDL37	115	973996	AC018494	631	1-1854
HNGOI12	128	1041375	AC003675	632	1-2128
HNGOI12	128	1041375	AC001228	633	1-2129
HNGOI12	128	1041375	AC013791	634	1-2132
HNHFM14	130	664507	AC020552	635	1-290
HNHFM14	130	664507	AC020552	636	1-96
HPJBK12	147	1011467	AC022033	637	1-2649
HPJBK12	147	1011467	AC013541	638	1-2649
HPJBK12	147	1011467	AC022033	639	1-190
HPJBK12	147	1011467	AC013541	640	1-190
HPRAL78	149	1352342	AC007783	641	1-2334 2508-3084 3578-3890 4198-4294 4376-4623 4712-5349 5369-6088 6527-7107 7298-7392 7730-7846 9147-9476 10487-10575 10791-11298 11485-11601 11783-13009 13207-13501 13540-13772 14439-14800 14923-14983

					15133-15355 15485-15653 16750-16805 16894-17078 17162-17219 18003-18089 21085-21146 21358-21501
HPRAL78	149	1352342	AC007783	642	1-308
HPRAL78	149	1352342	AC007783	643	1-1024
HRGBL78	153	910133	AL359541	644	1-254 2777-3307 3670-3823 4113-4385 4844-5381 5995-7365
HSAWD74	156	460527	AC004951	645	1-1651 1740-2593
HSAWD74	156	460527	AC004951	646	1-149
HSAWD74	156	460527	AC004951	647	1-5057 5082-8353 8404-8996
HTPCS72	177	854941	AL008639	648	1-106 1457-1595 1666-2484 2910-3006 3705-4147 4768-5141 5304-5536 5746-5874 7114-7241 7468-7711 7963-8746 9438-12408 12884-14976
HTPCS72	177	854941	AL008639	649	1-720
HTPIH83	178	919916	AL158821	650	1-1862 1880-3126

Tables 1D: The polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists could be used to treat the associated disease.

The present invention encompasses methods of detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating a disease or disorder. In preferred embodiments, the present invention encompasses a method of treating a gastrointestinal disease or disorder

comprising administering to a patient in which such detection, treatment, prevention, and/or amelioration is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) in an amount effective to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate the gastrointestinal disease or disorder.

In another embodiment, the present invention also encompasses methods of detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating a gastrointestinal disease or disorder; comprising administering to a patient combinations of the proteins, nucleic acids, or antibodies of the invention (or fragments or variants thereof), sharing similar indications as shown in the corresponding rows in Column 3 of Table 1D.

Table 1D provides information related to biological activities for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table 1D also provides information related to assays which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("cDNA Clone ID:") provides the unique clone identifier for each clone as previously described and indicated in Table 1A through Table 1D. The third column ("AA SEQ ID NO:Y") indicates the Sequence Listing SEQ ID Number for polypeptide sequences encoded by the corresponding cDNA clones (also as indicated in Tables 1A, Table 1B, and Table 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides (or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and also provides information pertaining to the various types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity.

Table 1D describes the use of, inter alia, FMAT technology for testing or demonstrating various biological activities. Fluorometric microvolume assay technology (FMAT) is a fluorescence-based system which provides a means to perform nonradioactive cell- and bead-based assays to detect activation of cell signal transduction pathways. This technology was designed specifically for ligand binding and immunological assays. Using this technology, fluorescent cells or beads at the bottom of the well are detected as localized areas of concentrated fluorescence using a data processing system. Unbound flurophore comprising the background signal is ignored, allowing for a wide variety of homogeneous assays. FMAT technology may be used for peptide ligand binding assays, immunofluorescence, apoptosis, cytotoxicity, and bead-based immunocapture assays. *See*, Miraglia S et. al., "Homogeneous cell and bead based assays for highthroughput screening using flourometric microvolume assay technology," Journal of Biomolecular Screening; 4:193-204 (1999). In particular, FMAT technology may be used to test,

confirm, and/or identify the ability of polypeptides (including polypeptide fragments and variants) to activate signal transduction pathways. For example, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides to upregulate production of immunomodulatory proteins (such as, for example, interleukins, GM-CSF, Rantes, and Tumor Necrosis factors, as well as other cellular regulators (e.g. insulin)).

Table 1D also describes the use of kinase assays for testing, demonstrating, or quantifying biological activity. In this regard, the phosphorylation and de-phosphorylation of specific amino acid residues (e.g. Tyrosine, Serine, Threonine) on cell-signal transduction proteins provides a fast, reversible means for activation and de-activation of cellular signal transduction pathways. Moreover, cell signal transduction via phosphorylation/de-phosphorylation is crucial to the regulation of a wide variety of cellular processes (e.g. proliferation, differentiation, migration, apoptosis, etc.). Accordingly, kinase assays provide a powerful tool useful for testing, confirming, and/or identifying polypeptides (including polypeptide fragments and variants) that mediate cell signal transduction events via protein phosphorylation. See e.g., Forrer, P., Tamaskovic R., and Jaussi, R. "Enzyme-Linked Immunosorbent Assay for Measurement of JNK, ERK, and p38 Kinase Activities" Biol. Chem. 379(8-9): 1101-1110 (1998).

Table 1D

Gene No.	cDNA Clone ID	AA SEQ ID NO: Y	Biological Activity	Exemplary Activity Assay
1	H2CBU83	300	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
2	H6EDC19	301	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that

				may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
3	HACBD91	302	Activation of transcription through cAMP response element (CRE) in pre-adipocytes.	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
3	HACBD91	302	Activation of transcription through cAMP response element in immune cells (such as T-cells).	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP and regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell

				line, which is a suspension culture of IL-2 dependent cytotoxic T cells.
3	HACBD91	302	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
3	HACBD91	302	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely

				generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
3	HACBD91	302	Activation of Endothelial Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.
3	HACBD91	302	Activation of transcription through CD28 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.
3	HACBD91	302	Activation of transcription through AP1 response element in	Assays for the activation of transcription through the AP1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely modified to test AP1-response element activity of polypeptides of the invention (including antibodies and

			immune cells (such as T-cells).	agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is an IL-2 and IL-4 responsive suspension-culture cell line.
3	HACBD91	302	Activation of transcription through CD28 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
3	HACBD91	302	Activation of transcription through NFAT response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Serfling et al., Biochim Biophys Acta 1498(1):1-18 (2000); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to

				these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
3	HACBD91	302	Activation of transcription through STAT6 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
3	HACBD91	302	Activation of transcription through NFKB response element in immune cells (such as T-cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
3	HACBD91	302	Activation of transcription through NFAT response element in	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or

			immune cells (such as natural killer cells).	routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
3	HACBD91	302	Activation of transcription through serum response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
4	HAGAQ26	303	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to

				these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
5	HAGDS35	304	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
6	HAJAN23	305	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J,

				288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
7	HAJBR69	306	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4lle cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.
7	HAJBR69	306	Production of GM-CSF	GM-CSF FMAT. GM-CSF is expressed by activated T cells, macrophages, endothelial cells, and fibroblasts. GM-CSF regulates differentiation and proliferation of granulocytes- macrophage progenitors and enhances antimicrobial activity in neutrophils, monocytes and macrophage. Additionally, GM-CSF plays an important role in the differentiation of dendritic cells and monocytes, and increases antigen presentation. GM-CSF is considered to be a proinflammatory cytokine. Assays for immunomodulatory proteins that promote the production of GM-CSF are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and modulate the growth and differentiation of leukocytes. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as GM-CSF, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and

				agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Ye et al., J Leukoc Biol (58(2):225-233, the contents of each of which are herein incorporated by reference in its entirety. Natural killer cells that may be used according to these assays are publicly available (e.g., through the ATCC) or may be isolated using techniques disclosed herein or otherwise known in the art. Natural killer (NK) cells are large granular lymphocytes that have cytotoxic activity but do bind antigen. NK cells show antibody-independent killing of tumor cells and also recognize antibody bound on target cells, via NK Fc receptors, leading to cell-mediated cytotoxicity.
8	HAMFE15	307	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
9	HAMGR28	308	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely

				modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
10	HAPOM49	309	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
11	HATBR65	310	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or

				routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
11	HATBR65	310	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
12	HAUAI83	311	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes.

				Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
13	HBAMB15	312	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
14	HBGBA69	313	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically

				active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
15	HBIAE26	314	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
16	HBINS58	315	Production of TNF alpha by dendritic cells	TNFa FMAT. Assays for immunomodulatory proteins produced by activated macrophages, T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for

				immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNFa), and the induction or inhibition of an inflammatory or cytotoxic response. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1198); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
16	HBINS58	315	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
17	HBNAW17	316	Activation of transcription through serum response	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through

			element in immune cells (such as T-cells).	the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.
17	HBNAW17	316	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
18	HCE2F54	317	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead

				et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4lle cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.
18	HCE2F54	317	Activation of transcription through NFKB response element in epithelial cells (such as HELA cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of epithhelial genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Kaltschmidt B, et al., Oncogene, 18(21):3213-3225 (1999); Beetz A, et al., Int J Radiat Biol, 76(11):1443-1453 (2000); Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Epithelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary epithelial cells that may be used according to these assays include the HELA cell line.
18	HCE2F54	317	Activation of transcription through NFKB response element in immune cells (such as the U937 human monocyte cell line).	This assay uses a NFKB response element (which will bind NFKB transcription factors) linked to a reporter gene to measure NFKB mediated transcription in the human monocyte cell line U937. NFKB is upregulated by cytokines and other factors and NFKB element activation leads to expression of immunomodulatory genes. Activation of NFKB in monocytes can play a role in immune responses. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Monocytic cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human monocyte cells that may be used according to these assays include the U937 cell line, which is cell line derived by Sundstrom and Nilsson in 1974 from malignant cells obtained from the pleural effusion of a patient with histiocytic

				lymphoma.
19	HCE3G69	318	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
19	HCE3G69	318	Production of IL-10 and activation of T-cells.	Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.
20	HCE5F43	319	Stimulation of insulin secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or

			from pancreatic beta cells.	antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
21	HCEFB80	320	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.
21	HCEFB80	320	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the

				invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
22	HCEWE20	321	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
22	HCEWE20	321	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Rolfe BE, et al., Atherosclerosis, 149(1):99-110 (2000); Panettieri RA Jr, et al., J Immunol, 154(5):2358-2365 (1995);

				and, Grunstein MM, et al., Am J Physiol Lung Cell Mol Physiol, 278(6):L1154-L1163 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include Aortic Smooth Muscle Cells (AOSMC); such as bovine AOSMC.
23	HCGMD59	322	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al:, Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
24	HCNDR47	323	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly

				available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
25	HCNSM70	324	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
26	HCUIM65	325	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of

				each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
26	HCUIM65	325	Activation of transcription through cAMP response element (CRE) in pre-adipocytes.	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
26	HCUIM65	325	Activation of transcription through serum response element in pre-adipocytes.	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely

				generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
26	HCUIM65	325	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
26	HCUIM65	325	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson

				et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
26	HCUIM65	325	Activation of transcription through NFAT response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
26	HCUIM65	325	Activation of transcription through NFKB response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFkB signaling pathway in HMC-1 human mast cell line. Activation of NFkB in mast cells has been linked to production of certain cytokines, such as IL-6 and IL-9. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Stassen et al, J Immunol 166(7):4391-8 (2001); and Marquardt and Walker, J Allergy Clin Immunol 105(3):500-5

				(2000), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
26	HCUIM65	325	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to bind the serum response factor and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells, such as the MOLT4, that may be used according to these assays are publicly available (e.g., through the ATCC).
26	HCUIM65	325	Activation of transcription through STAT6 response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad.Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat natural killer cells that may be used according to these assays are publicly available (e.g., through the ATCC).
26	HCUIM65	325	Activation of transcription	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of

			through GAS response element in immune cells (such as T-cells).	polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the SUPT cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).
26	HCUIM65	325	Activation of transcription through NFAT response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
26	HCUIM65	325	Activation of transcription through serum response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117

				(1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
27	HCWDS72	326	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
28	HCWKC15	327	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of

				each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
28	HCWKC15	327	Activation of transcription through cAMP response element (CRE) in pre-adipocytes.	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
28	HCWKC15	327	Activation of transcription through serum response element in pre-adipocytes.	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely

				generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
28	HCWKC15	327	Activation of transcription through GAS response element in immune cells (such as eosinophils).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate gene expression (commonly via STAT transcription factors) involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995); the contents of each of which are herein incorporated by reference in its entirety. Moreover, exemplary assays that may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate or inhibit activation of immune cells include assays disclosed and/or cited in: Mayumi M., "EoL-1, a human eosinophilic cell line" Leuk Lymphoma; Jun;7(3):243-50 (1992); Bhattacharya S, "Granulocyte macrophage colony-stimulating factor and interleukin-5 activate STAT5 and induce CIS1 mRNA in human peripheral blood eosinophils" Am J Respir Cell Mol Biol; Mar;24(3):312-6 (2001); and, Du J, et al., "Engagement of the CrkL adapter in interleukin-5 signaling in eosinophils" J Biol Chem; Oct 20;275(42):33167-75 (2000); the contents of each of which are herein incorporated by reference in its entirety. Exemplary cells that may be used according to these assays include eosinophils. Eosinophils are a type of immune cell important in the late stage of allergic reactions; they are recruited to tissues and mediate the inflammtory response of late stage allergic reaction. Increases in GAS mediated transcription in eosinophils is typically a result of STAT activation, normally a direct consequence of interleukin or other cytokine receptor stimulation (e.g. IL3, IL5 or GMCSF).
28	HCWKC15	327	Activation of transcription through NFKB response element in immune cells	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention)

			(such as EOL1 cells).	include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. For example, a reporter assay (which measures increases in transcription inducible from a NFkB responsive element in EOL-1 cells) may link the NFKB element to a repeorter gene and binds to the NFKB transcription factor, which is upregulated by cytokines and other factors. Exemplary immune cells that may be used according to these assays include eosinophils such as the human EOL-1 cell line of eosinophils. Eosinophils are a type of immune cell important in the allergic responses; they are recruited to tissues and mediate the inflammtory response of late stage allergic reaction. Eol-1 is a human eosinophil cell line.
28	HCWKC15	327	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
28	HCWKC15	327	Activation of transcription through NFAT response element in immune cells	This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions.

			(such as mast cells).	Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
28	HCWKC15	327	Activation of transcription through NFKB response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFkB signaling pathway in HMC-1 human mast cell line. Activation of NFkB in mast cells has been linked to production of certain cytokines, such as IL-6 and IL-9. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Stassen et al, J Immunol 166(7):4391-8 (2001); and Marquardt and Walker, J Allergy Clin Immunol 105(3):500-5 (2000), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
28	HCWKC15	327	Activation of transcription through STAT6 response element in immune cells	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element in immune cells (such as in the human HMC-1 mast cell line) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity

			(such as mast cells).	of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Sherman, Immunol Rev 179:48-56 (2001); Malaviya and Uckun, J Immunol 168:421-426 (2002); Masuda et al., J Biol Chem 275(38):29331-29337 (2000); and Masuda et al., J Biol Chem 276:26107-26113 (2001), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
28	HCWKC15	327	Activation of transcription through NFKB response element in immune cells (such as basophils).	This reporter assay measures activation of the NFkB signaling pathway in Ku812 human basophil cell line. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which are herein incorporated by reference in its entirety. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate into mature basophils.
28	HCWKC15	327	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to bind the serum response factor and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may

				be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells, such as the MOLT4, that may be used according to these assays are publicly available (e.g., through the ATCC).
28	HCWKC15	327	Activation of transcription through NFKB response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
28	HCWKC15	327	Activation of transcription through STAT6 response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat natural killer cells that may be used according to these assays are publicly available (e.g., through the ATCC).
28	HCWKC15	327	Activation of transcription through AP1 response	Assays for the activation of transcription through the AP1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely

			element in immune cells (such as T-cells).	modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is an IL-2 and IL-4 responsive suspension-culture cell line.
28	HCWKC15	327	Activation of transcription through CD28 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
28	HCWKC15	327	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the SUPT cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).

28	HCWKC15	327	Activation of transcription through NFAT response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Serfling et al., Biochim Biophys Acta 1498(1):1-18 (2000); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
28	HCWKC15	327	Activation of transcription through NFKB response element in immune cells (such as T-cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
28	HCWKC15	327	Activation of transcription through NFAT response element in immune cells	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including

			(such as natural killer cells).	antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
28	HCWKC15	327	Activation of transcription through serum response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
29	HDHEB60	328	Activation of transcription through cAMP response element (CRE) in pre-adipocytes.	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem

				273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
29	HDHEB60	328	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
29	HDHEB60	328	Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to meaure the upregulation of cell surface VCAM-1 expresssion in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.
29	HDHEB60	328	Activation of transcription	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the

			through STAT6 response element in immune cells (such as natural killer cells).	ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat natural killer cells that may be used according to these assays are publicly available (e.g., through the ATCC).
29	HDHEB60	328	Activation of transcription through AP1 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the AP1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is an IL-2 and IL-4 responsive suspension-culture cell line.
29	HDHEB60	328	Activation of transcription through CD28 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents

				of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
29	HDHEB60	328	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the SUPT cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).
29	HDHEB60	328	Activation of transcription through NFAT response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Serfling et al., Biochim Biophys Acta 1498(1):1-18 (2000); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
29	HDHEB60	328	Activation of transcription through STAT6	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention)

			response element in immune cells (such as T-cells).	to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
29	HDHEB60	328	Activation of transcription through NFKB response element in immune cells (such as T-cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
29	HDHEB60	328	Activation of transcription through NFAT response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999);

				and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
30	HDPBA28	329	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
30	HDPBA28	329	Production of IL-10 and activation of T-cells.	Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are

				generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.
31	HDPCL63	330	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
32	HDPCO25	331	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ohtani KI, et al., Endocrinology, 139(1):172-8 (1998); Krautheim A, et al, Exp Clin Endocrinol Diabetes, 107 (1):29-34 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci.

				USA 78: 4339-4343, 1981.
32	HDPCO25	331	Activation of transcription through NFKB response element in immune cells (such as T-cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
33	HDPFP29	332	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
34	HDPGT01	333	Regulation of transcription through the FAS promoter element in	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in

			hepatocytes	livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
35	HDPHI51	334	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
35	HDPHI51	334	Activation of transcription through STAT6 response element in immune cells (such as T-	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998);

			cells).	Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
36	HDPJM30	335	Production of MCP-1	MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
36	HDPJM30	335	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368

				(1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
37	HDPMM88	336	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
38	HDPOJ08	337	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that

				may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
39	HDPPN86	338	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
40	HDPSB18	339	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1

				cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
40	HDPSB18	339	Production of IL-10 and downregulation of immune responses	IL-10 FMAT. Assays for immunomodulatory proteins produced by activated T cells, B cells, and monocytes that exhibit anti-inflammatory activity and downregulate monocyte/macrophage function and expression of cytokines are well known in the art and may be used or routinely modified to assess the ability of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, and modulate immune cell function and cytokine production. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-10, and the downmodulation of immune responses. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Koning et al., Cytokine 9(6):427-436 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
41	HDPSH53	340	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete

				insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
42	HDPSP01	341	Production of MCP-1	MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
42	HDPSP01	341	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon,

				somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
43	HDPSP54	342	Activation of Endothelial Cell JNK Signaling Pathway.	Kinase assay. JNK kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK kinase activity that may be used or routinely modified to test JNK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.
43	HDPSP54	342	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly

				glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
43	HDPSP54	342	Production of IL-10 and activation of T-cells.	Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.
44	HDPUW68	343	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
44	HDPUW68	343	Activation of transcription	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention

			through serum response element in immune cells (such as T-cells).	(including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.
44	HDPUW68	343	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
44	HDPUW68	343	Activation of Skeletal Mucle Cell PI3 Kinase Signalling Pathway	Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for PI3 kinase signal transduction that regulate glucose metabolism and cell survivial are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention)

				include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.
45	HDPXY01	344	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
46	HDTBD53	345	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor

				beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
47	HDTBV77	346	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
48	HDTDQ23	347	Endothelial Cell Apoptosis	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Induction of apoptosis in endothelial cells supporting the vasculature of tumors is associated with tumor regression due to loss of tumor blood supply. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2):

				75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.
48	HDTDQ23	347	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
49	HE2DE47	348	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS

				Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
50	HE2NV57	349	Activation of T-Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit immune cell (e.g. T-cell) proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.
50	HE2NV57	349	Activation of transcription through AP1 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the AP1 response element are known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell

				line with cytotoxic activity.
50	HE2NV57	349	Activation of transcription through cAMP response element in immune cells (such as T-cells).	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP and regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.
50	HE2NV57	349	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.
50	HE2NV57	349	Activation of transcription through serum response element in immune cells (such as T-	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al.,

			cells).	Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.
50	HE2NV57	349	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
50	HE2NV57	349	Activation of transcription through CD28 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be

				used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.
51	HE2PH36	350	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
52	HE8DS15	351	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
52	HE8DS15	351	Regulation of	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or

			transcription of Malic Enzyme in adipocytes	routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
53	HE9HY07	352	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
53	HE9HY07	352	Regulation of transcription through the FAS promoter	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. *FAS promoter is*

			element in hepatocytes	regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
54	HEOMQ63	353	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
55	HEPAB80	354	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the

				invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
55	HEPAB80	354	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ohtani KI, et al., Endocrinology, 139(1):172-8 (1998); Krautheim A, et al, Exp Clin Endocrinol Diabetes, 107 (1):29-34 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
56	HFABH95	355	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li,

				M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S.et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
56	HFABH95	355	Upregulation of CD69 and activation of T cells	CD69 FMAT. CD69 is an activation marker that is expressed on activated T cells, B cells, and NK cells. CD69 is not expressed on resting T cells, B cells, or NK cells. CD69 has been found to be associated with inflammation. Assays for immunomodulatory proteins expressed in T cells, B cells, and leukocytes are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD69, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Ferenczi et al., J Autoimmun 14(1):63-78 (200); Werfel et al., Allergy 52(4):465-469 (1997); Taylor-Fishwick and Siegel, Eur J Immunol 25(12):3215-3221 (1995); and Afetra et al., Ann Rheum Dis 52(6):457-460 (1993), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
57	HFAEF57	356	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the

				invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
58	HFCEB37	357	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
59	HFFAD59	358	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora,

				S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
59	HFFAD59	358	Activation of transcription through AP1 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the AP1 response element are known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.
59	HFFAD59	358	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension

				culture of T cells with cytotoxic activity.
60	HFGAD82	359	Activation of transcription through AP1 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the AP1 response element are known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the HT2 cell line, which is an IL-2 dependent suspension culture cell line that also responds to IL-4.
60	HFGAD82	359	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
61	HFIUR10	360	Regulation of viability and proliferation of pancreatic beta	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable

			cells.	cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ohtani KI, et al., Endocrinology, 139(1):172-8 (1998); Krautheim A, et al, Exp Clin Endocrinol Diabetes, 107 (1):29-34 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
62	HFTBM50	361	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
62	HFTBM50	361	Production of IL-10 and activation of T-	Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of

			cells.	T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.
63	HFTDZ36	362	Protection from Endothelial Cell Apoptosis.	Caspase Apoptosis Rescue. Assays for caspase apoptosis rescue are well known in the art and may be used or routinely modified to assess the ability of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to inhibit caspase protease-mediated apoptosis. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis rescue of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Romeo et al., Cardiovasc Res 45(3): 788-794 (2000); Messmer et al., Br J Pharmacol 127(7): 1633-1640 (1999); and J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.
63	HFTDZ36	362	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995);

				and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
64	HFXBL33	363	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
65	HFXJX44	364	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the

				invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
66	HFXKT05	365	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
67	HGBHI35	366	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of

				which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
68	HGLAF75	367	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
68	HGLAF75	367	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by

				reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
68	HGLAF75	367	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
69	HHENV10	368	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65

				(1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
70	HHGCG53	369	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
71	HHGCM76	370	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated.

				Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
71	HHGCM76	370	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J, 15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).
72	HHPEN62	371	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
73	HJABB94	372	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by

				FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
74	HJACG30	373	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.
74	HJACG30	373	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the

				invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
75	HJBCY35	374	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
75	HJBCY35	374	Activation of Skeletal Mucle Cell PI3 Kinase Signalling Pathway	Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for PI3 kinase signal transduction that regulate glucose metabolism and cell survivial are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used

				according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.
76	HJPAD75	375	Activation of T-Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit immune cell (e.g. T-cell) proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.
76	HJPAD75	375	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting

				cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
76	HJPAD75	375	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
77	HKABZ65	376	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using

				techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
77	HKABZ65	376	Activation of Endothelial Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.
77	HKABZ65	376	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly

				glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
78	HKACB56	377	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
78	HKACB56	377	Production of IL-5	IL-5 FMAT. Assays for immunomodulatory proteins secreted by TH2 cells, mast cells, basophils, and eosinophils that stimulate eosinophil function and B cell Ig production and promote polarization of CD4+ cells into TH2 cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, stimulate immune cell function, modulate B cell Ig production, modulate immune cell polarization, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-5, and the stimulation of eosinophil function and B cell Ig production. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Ohshima et al., Blood 92(9):3338-3345 (1998); Jung et al., Eur J Immunol 25(8):2413-2416 (1995); Mori et al., J Allergy Clin Immunol 106(1 Pt 2):558-564 (2000); and Koning et al., Cytokine 9(6):427-436 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated

				immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
78	HKACB56	377	Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to meaure the upregulation of cell surface VCAM-1 expresssion in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.
78	HKACB56	377	Activation of Endothelial Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.
78	HKACB56	377	Upregulation of CD152 and activation of T cells	CD152 FMAT. CD152 (a.k.a. CTLA-4) expression is restricted to activated T cells. CD152 is a negative regulator of T cell proliferation. Reduced CD152 expression has been linked to hyperproliferative and autoimmune diseases. Overexpression of CD152 may lead to impaired immunoresponses. Assays for immunomodulatory proteins important in the maintenance of T cell homeostasis and expressed almost exclusively on CD4+ and CD8+ T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, maintain T cell homeostasis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for

				immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD152, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); McCoy et al., Immunol Cell Biol 77(1):1-10 (1999); Oostervegal et al., Curr Opin Immunol 11(3):294-300 (1999); and Saito T, Curr Opin Immunol 10(3):313-321 (1998), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
79	HKACD58	378	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
79	HKACD58	378	IL-2 in Human T cells	

79	HKACD58	378	Activation of transcription through serum response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
80	HKAEV06	379	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ohtani KI, et al., Endocrinology, 139(1):172-8 (1998); Krautheim A, et al, Exp Clin Endocrinol Diabetes, 107 (1):29-34 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
80	HKAEV06	379	Activation of transcription through AP1 response	Assays for the activation of transcription through the AP1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely

			element in immune cells (such as T-cells).	modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is an IL-2 and IL-4 responsive suspension-culture cell line.
81	HKAFT66	380	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
81	HKAFT66	380	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of

				Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
81	HKAFT66	380	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
81	HKAFT66	380	Activation of transcription through NFAT response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10

				(1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
82	HKB1E57	381	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
83	HKFBC53	382	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998);

				Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
84	HKGDL36	383	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
85	HKISB57	384	Activation of JNK Signaling Pathway in immune cells (such as eosinophils).	Kinase assay. JNK kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK kinase activity that may be used or routinely modified to test JNK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Exemplary cells that may be used according to these assays include eosinophils. Eosinophils are important in the late stage of allergic reactions; they are

				recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Moreover, exemplary assays that may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate signal transduction, cell proliferation, activation, or apoptosis in eosinophils include assays disclosed and/or cited in: Zhang JP, et al., "Role of caspases in dexamethasone-induced apoptosis and activation of c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase in human eosinophils" Clin Exp Immunol; Oct;122(1):20-7 (2000); Hebestreit H, et al., "Disruption of fas receptor signaling by nitric oxide in eosinophils" J Exp Med; Feb 2;187(3):415-25 (1998); J Allergy Clin Immunol 1999 Sep;104(3 Pt 1):565-74; and, Sousa AR, et al., "In vivo resistance to corticosteroids in bronchial asthma is associated with enhanced phosyphorylation of JUN N-terminal kinase and failure of prednisolone to inhibit JUN N-terminal kinase phosphorylation" J Allergy Clin Immunol; Sep;104(3 Pt 1):565-74 (1999); the contents of each of which are herein incorporated by reference in its entirety.
85	HKISB57	384	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
86	HKMLM11	385	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating

				skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
87	HKMMW74	386	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
88	HLDON23	387	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the

				contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4lle cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.
88	HLDON23	387	Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to meaure the upregulation of cell surface VCAM-1 expresssion in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.
88	HLDON23	387	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J, 15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).
88	HLDON23	387	Production of IL-10 and activation of T-cells.	Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety.

				Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.
89	HLDQR62	388	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
89	HLDQR62	388	Activation of transcription through cAMP response element in immune cells (such as T-cells).	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP and regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell

				line, which is a suspension culture of IL-2 dependent cytotoxic T cells.
90	HLDQU79	389	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
90	HLDQU79	389	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.
91	HLHAL68	390	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically

				active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
92	HLIBD68	391	Production of TNF alpha by dendritic cells	TNFa FMAT. Assays for immunomodulatory proteins produced by activated macrophages, T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNFa), and the induction or inhibition of an inflammatory or cytotoxic response. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1198); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
92	HLIBD68	391	Production of MIP1alpha	MIP-1alpha FMAT. Assays for immunomodulatory proteins produced by activated dendritic cells that upregulate monocyte/macrophage and T cell chemotaxis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate chemotaxis, and modulate T cell differentiation. Exemplary assays that test for immunomodulatory proteins evaluate the production of chemokines, such as macrophage inflammatory protein 1 alpha (MIP-1a), and the

				activation of monocytes/macrophages and T cells. Such assays that may be used or routinely modified to test immunomodulatory and chemotaxis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); Drakes et al., Transp Immunol 8(1):17-29 (2000); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
92	HLIBD68	391	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
92	HLIBD68	391	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by

				glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
93	HLICQ90	392	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.
93	HLICQ90	392	Production of TNF alpha by dendritic cells	TNFa FMAT. Assays for immunomodulatory proteins produced by activated macrophages, T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNFa), and the induction or inhibition of an inflammatory or cytotoxic response. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach"

				Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1198); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
93	HLICQ90	392	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
93	HLICQ90	392	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995);

				and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
94	HLTHR66	393	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
95	HLTIP94	394	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to

				these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
96	HLWAA17	395	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
96	HLWAA17	395	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J, 15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).
97	HLYAC95	396	Production of IFNgamma using a T cells	IFNgamma FMAT. IFNg plays a central role in the immune system and is considered to be a proinflammatory cytokine. IFNg promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a variety of inflammatory

				activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFNg), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
97	HLYAC95	396	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
98	HMADK33	397	Regulation of transcription	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including

			through the PEPCK promoter in hepatocytes	antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4lle cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.
99	HMAMI15	398	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
99	HMAMI15	398	Upregulation of CD152 and activation of T cells	CD152 FMAT. CD152 (a.k.a. CTLA-4) expression is restricted to activated T cells. CD152 is a negative regulator of T cell proliferation. Reduced CD152 expression has been linked to hyperproliferative and autoimmune diseases. Overexpression of CD152 may lead to impaired immunoresponses. Assays for immunomodulatory proteins important in the maintenance of T cell

				homeostasis and expressed almost exclusively on CD4+ and CD8+ T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, maintain T cell homeostasis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD152, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); McCoy et al., Immunol Cell Biol 77(1):1-10 (1999); Oostervegal et al., Curr Opin Immunol 11(3):294-300 (1999); and Saito T, Curr Opin Immunol 10(3):313-321 (1998), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
100	HMCFY13	399	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous

				substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
101	HMDAB56	400	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4lle cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.
102	HMEED18	401	Production of IL6 by primary human aortic smooth muscle or normal human dermal fibroblast cells (without or with costimulation with TNFalpha).	Assay to measure regulation of production of Interleukin-6 (IL-6) by either human aortic smooth muscle cells or normal human dermal fibroblasts minus or plus costimulation with TNFalpha (TNFa). Human aortic smooth muscle cells or normal human dermal fibroblasts may be obtained from commercial sources; these cells are important structural and functional components of blood vessels and connective tissue, respectiviely. Interleukin-6 (IL-6) is a key molecule in chronic inflammation and has been implicated in the progression of atherosclerosis, stroke, arthritis and other vascular and inflammatory diseases. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and production of IL-6.
102	HMEED18	401	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely

				modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
102	HMEED18	401	Upregulation of CD69 and activation of T cells	CD69 FMAT. CD69 is an activation marker that is expressed on activated T cells, B cells, and NK cells. CD69 is not expressed on resting T cells, B cells, or NK cells. CD69 has been found to be associated with inflammation. Assays for immunomodulatory proteins expressed in T cells, B cells, and leukocytes are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD69, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Ferenczi et al., J Autoimmun 14(1):63-78 (200); Werfel et al., Allergy 52(4):465-469 (1997); Taylor-Fishwick and Siegel, Eur J Immunol 25(12):3215-3221 (1995); and Afetra et al., Ann Rheum Dis 52(6):457-460 (1993), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
103	HMEFT54	402	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase

				apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
104	HMEGF92	403	Production of ICAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	Endothelial cells, which are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used in ICAM production assays include human umbilical vein endothelial cells (HUVEC), and are available from commercial sources. The expression of ICAM (CD54),a intergral membrane protein, can be upregulated by cytokines or other factors, and ICAM expression is important in mediating immune and endothelial cell interactions leading to immune and inflammatory responses. Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Rolfe BE, et al., Atherosclerosis, 149(1):99-110 (2000); Panettieri RA Jr, et al., J Immunol, 154(5):2358-2365 (1995); and, Grunstein MM, et al., Am J Physiol Lung Cell Mol Physiol, 278(6):L1154-L1163 (2000), the contents of each of which is herein incorporated by reference in its entirety.
104	HMEGF92	403	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed

				in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
105	HMSDL37	404	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
106	HMSFI26	405	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes.

				Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
107	HMVBS81	406	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
108	HMWDC28	407	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the

				invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
109	HMWFT65	408	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
110	HNEEE24	409	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes.

				Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
111	HNFFC43	410	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
111	HNFFC43	410	Proliferation of	Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are

			immune cells (such as the HMC-1 human mast cell line)	well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of eosinophil cells and cell lines. For example, the CellTiter-Gloδ Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Mast cells are found in connective and mucosal tissues throughout the body. Mast cell activation (via immunoglobulin E -antigen, promoted by T helper cell type 2 cytokines) is an important component of allergic disease. Dysregulation of mast cell apoptosis may play a role in allergic disease and mast cell tumor survival. Mast cell lines that may be used according to these assays are publicly available and/or may be routinely generated. Exemplary mast cells that may be used according to these assays include HMC-1, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
111	HNFFC43	410	Activation of T-Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit immune cell (e.g. T-cell) proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.
111	HNFFC43	410	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998);

				Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
112	HNFIY77	411	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
113	HNFJF07	412	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the

				invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
113	HNFJF07	412	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
113	HNFJF07	412	Activation of transcription through serum response element in immune cells (such as T-	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al.,

			cells).	Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.
113	HNFJF07	412	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
114	HNGFR31	413	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that

				may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
115	HNGIJ31	414	Activation of transcription through cAMP response element in immune cells (such as T-cells).	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP and regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.
115	HNGIJ31	414	Production of MCP-1	MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.

115	HNGIJ31	414	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
115	HNGIJ31	414	Activation of Skeletal Mucle Cell PI3 Kinase Signalling Pathway	Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for PI3 kinase signal transduction that regulate glucose metabolism and cell survivial are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.
116	HNGJE50	415	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly

				regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
116	HNGJE50	415	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
117	HNGND37	416	Regulation of transcription	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including

			through the PEPCK promoter in hepatocytes	antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4lle cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.
118	HNGOI12	417	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
118	HNGOI12	417	Production of IL-10 and activation of T-cells.	Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides

				and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.
119	HNHEU93	418	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
120	HNHFM14	419	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or

				antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
121	HNHNB29	420	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4lle cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.
122	HNHOD46	421	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys

				Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
122	HNHOD46	421	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known *in the art* and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
122	HNHOD46	421	Activation of transcription through cAMP response element (CRE) in pre-adipocytes.	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to

				test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
122	HNHOD46	421	Activation of transcription through serum response element in pre-adipocytes.	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
122	HNHOD46	421	Activation of transcription through cAMP response element in immune cells (such as T-cells).	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP and regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its

				entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.
122	HNHOD46	421	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.
122	HNHOD46	421	Production of MIP1alpha	MIP-1alpha FMAT. Assays for immunomodulatory proteins produced by activated dendritic cells that upregulate monocyte/macrophage and T cell chemotaxis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate chemotaxis, and modulate T cell differentiation. Exemplary assays that test for immunomodulatory proteins evaluate the production of chemokines, such as macrophage inflammatory protein 1 alpha (MIP-1a), and the activation of monocytes/macrophages and T cells. Such assays that may be used or routinely modified to test immunomodulatory and chemotaxis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); Drakes et al., Transp Immunol 8(1):17-29 (2000); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
122	HNHOD46	421	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6

				induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
122	HNHOD46	421	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.

122	HNHOD46	421	Activation of transcription through NFAT response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
122	HNHOD46	421	Activation of transcription through cAMP response element in immune cells (such as T-cells).	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, bind to CREB transcription factor, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.
122	HNHOD46	421	Activation of transcription through NFAT	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to

			response in immune cells (such as T-cells).	regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Serfling et al., Biochim Biophys Acta 1498(1):1-18 (2000); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.
122	HNHOD46	421	Activation of transcription through NFKB response element in immune cells (such as basophils).	This reporter assay measures activation of the NFkB signaling pathway in Ku812 human basophil cell line. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which are herein incorporated by reference in its entirety. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate into mature basophils.
122	HNHOD46	421	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl

				Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the MOLT4 cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).
122	HNHOD46	421	Activation of transcription through NFKB response element in immune cells (such as T-cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the MOLT4, that may be used according to these assays are publicly available (e.g., through the ATCC).
122	HNHOD46	421	Activation of transcription through NFKB response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
122	HNHOD46	421	Activation of transcription through AP1 response element in immune cells	Assays for the activation of transcription through the AP1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988);

			(such as T-cells).	Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is an IL-2 and IL-4 responsive suspension-culture cell line.
122	HNHOD46	421	Activation of transcription through CD28 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
122	HNHOD46	421	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the SUPT cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).
122	HNHOD46	421	Activation of transcription	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of

			through NFAT response element in immune cells (such as T-cells).	polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Serfling et al., Biochim Biophys Acta 1498(1):1-18 (2000); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
122	HNHOD46	421	Activation of transcription through STAT6 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
122	HNHOD46	421	Activation of transcription through NFKB response element in immune cells (such as T-	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol

			cells).	216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.
122	HNHOD46	421	Activation of transcription through serum response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
123	HNTBI26	422	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell

				insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
124	HNTBL27	423	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
124	HNTBL27	423	Production of IL-10 and activation of T-cells.	Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete

				IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.
125	HNTCE26	424	Production of TNF alpha by dendritic cells	TNFa FMAT. Assays for immunomodulatory proteins produced by activated macrophages, T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNFa), and the induction or inhibition of an inflammatory or cytotoxic response. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1198); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
125	HNTCE26	424	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1

				cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
125	HNTCE26	424	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J, 15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).
125	HNTCE26	424	Upregulation of CD69 and activation of T cells	CD69 FMAT. CD69 is an activation marker that is expressed on activated T cells, B cells, and NK cells. CD69 is not expressed on resting T cells, B cells, or NK cells. CD69 has been found to be associated with inflammation. Assays for immunomodulatory proteins expressed in T cells, B cells, and leukocytes are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD69, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Ferenczi et al., J Autoimmun 14(1):63-78 (200); Werfel et al., Allergy 52(4):465-469 (1997); Taylor-Fishwick and Siegel, Eur J Immunol 25(12):3215-3221 (1995); and Afetra et al., Ann Rheum Dis 52(6):457-460 (1993), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
126	HNTNI01	425	Regulation of transcription via DMEF1 response	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The

			element in adipocytes and pre-adipocytes	DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
126	HNTNI01	425	Activation of transcription through cAMP response element (CRE) in pre-adipocytes.	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.

126	HNTNI01	425	Activation of transcription through serum response element in pre-adipocytes.	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
126	HNTNI01	425	Activation of transcription through GAS response element in immune cells (such as eosinophils).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate gene expression (commonly via STAT transcription factors) involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995); the contents of each of which are herein incorporated by reference in its entirety. Moreover, exemplary assays that may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate or inhibit activation of immune cells include assays disclosed and/or cited in: Mayumi M., "EoL-1, a human eosinophilic cell line" Leuk Lymphoma; Jun;7(3):243-50 (1992); Bhattacharya S, "Granulocyte macrophage colony-stimulating factor and interleukin-5 activate STAT5 and induce CIS1 mRNA in human peripheral blood eosinophils" Am J Respir Cell Mol Biol; Mar;24(3):312-6 (2001); and, Du J, et al., "Engagement of the CrkL adapter in interleukin-5 signaling in eosinophils" J Biol Chem; Oct 20;275(42):33167-75 (2000); the contents of each of which are herein incorporated by reference in its entirety. Exemplary cells that may be used according to these assays include eosinophils. Eosinophils are a type of immune cell important in the late stage of allergic

				reactions; they are recruited to tissues and mediate the inflammtory response of late stage allergic reaction. Increases in GAS mediated transcription in eosinophils is typically a result of STAT activation, normally a direct consequence of interleukin or other cytokine receptor stimulation (e.g. IL3, IL5 or GMCSF).
126	HNTNI01	425	Activation of transcription through NFKB response element in immune cells (such as EOL1 cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. For example, a reporter assay (which measures increases in transcription inducible from a NFkB responsive element in EOL-1 cells) may link the NFKB element to a repeorter gene and binds to the NFKB transcription factor, which is upregulated by cytokines and other factors. Exemplary immune cells that may be used according to these assays include eosinophils such as the human EOL-1 cell line of eosinophils. Eosinophils are a type of immune cell important in the allergic responses; they are recruited to tissues and mediate the inflammtory response of late stage allergic reaction. Eol-1 is a human eosinophil cell line.
126	HNTNI01	425	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used

				according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
126	HNTNI01	425	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
126	HNTNI01	425	Activation of transcription through NFAT response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are

				publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
126	HNTNI01	425	Activation of transcription through NFKB response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFkB signaling pathway in HMC-1 human mast cell line. Activation of NFkB in mast cells has been linked to production of certain cytokines, such as IL-6 and IL-9. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Stassen et al, J Immunol 166(7):4391-8 (2001); and Marquardt and Walker, J Allergy Clin Immunol 105(3):500-5 (2000), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
126	HNTNI01	425	Activation of transcription through STAT6 response element in immune cells (such as mast cells).	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element in immune cells (such as in the human HMC-1 mast cell line) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Sherman, Immunol Rev 179:48-56 (2001); Malaviya and Uckun, J Immunol 168:421-426 (2002); Masuda et al., J Biol Chem 275(38):29331-29337 (2000); and Masuda et al., J Biol Chem 276:26107-26113 (2001), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line

				established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
126	HNTNI01	425	Activation of transcription through NFKB response element in immune cells (such as basophils).	This reporter assay measures activation of the NFkB signaling pathway in Ku812 human basophil cell line. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which are herein incorporated by reference in its entirety. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate into mature basophils.
126	HNTNI01	425	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to bind the serum response factor and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells, such as the MOLT4, that may be used according to these assays are publicly available (e.g., through the ATCC).
126	HNTNI01	425	Activation of transcription through STAT6 response element in	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to

			immune cells (such as natural killer cells).	test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat natural killer cells that may be used according to these assays are publicly available (e.g., through the ATCC).
126	HNTNI01	425	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the SUPT cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).
126	HNTNI01	425	Activation of transcription through NFAT response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to

				these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
127	HODDF13	426	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
127	HODDF13	426	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral

				blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
127	HODDF13	426	Activation of transcription through NFAT response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
128	HODDN92	427	Production of MIP1alpha	MIP-1alpha FMAT. Assays for immunomodulatory proteins produced by activated dendritic cells that upregulate monocyte/macrophage and T cell chemotaxis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate chemotaxis, and modulate T cell differentiation. Exemplary assays that test for immunomodulatory proteins evaluate the production of chemokines, such as macrophage inflammatory protein 1 alpha (MIP-1a), and the activation of monocytes/macrophages and T cells. Such assays that may be used or routinely modified to test immunomodulatory and chemotaxis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); Drakes et al., Transp Immunol 8(1):17-29 (2000); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in

				suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
128	HODDN92	427	Production of MCP-1	MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
128	HODDN92	427	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using

				techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
128	HODDN92	427	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
128	HODDN92	427	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays

				include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
128	HODDN92	427	Activation of transcription through NFAT response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
128	HODDN92	427	Activation of Endothelial Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.

129	HOFMQ33	428	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ohtani KI, et al., Endocrinology, 139(1):172-8 (1998); Krautheim A, et al, Exp Clin Endocrinol Diabetes, 107 (1):29-34 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
129	HOFMQ33	428	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to bind the serum response factor and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells, such as the MOLT4, that may be used according to these assays are publicly available (e.g., through the ATCC).
130	HOFOC73	429	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the

				invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
131	HOQBJ82	430	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
132	HOSBY40	431	Regulation of transcription through the FAS promoter element in	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in

			hepatocytes	livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
133	HOSDJ25	432	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Rolfe BE, et al., Atherosclerosis, 149(1):99-110 (2000); Panettieri RA Jr, et al., J Immunol, 154(5):2358-2365 (1995); and, Grunstein MM, et al., Am J Physiol Lung Cell Mol Physiol, 278(6):L1154-L1163 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include Aortic Smooth Muscle Cells (AOSMC); such as bovine AOSMC.
133	HOSDJ25	432	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Kráutheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly

				available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
133	HOSDJ25	432	Activation of transcription through NFAT response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
134	HPEAD79	433	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle.. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al.,

				Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
135	HPIBO15	434	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
135	HPIBO15	434	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and

				diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
136	HPJBI33	435	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
137	HPJBK12	436	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of

				Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
137	HPJBK12	436	Regulation of apoptosis of immune cells (such as mast cells).	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate caspase protease-mediated apoptosis in immune cells (such as, for example, in mast cells). Mast cells are found in connective and mucosal tissues throughout the body, and their activation via immunoglobulin E -antigen, promoted by T helper cell type 2 cytokines, is an important component of allergic disease. Dysregulation of mast cell apoptosis may play a role in allergic disease and mast cell tumor survival. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity induced by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Masuda A, et al., J Biol Chem, 276(28):26107-26113 (2001); Yeatman CF 2nd, et al., J Exp Med, 192(8):1093-1103 (2000);Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Immune cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary immune cells that may be used according to these assays include mast cells such as the HMC human mast cell line.
137	HPJBK12	436	Activation of Endothelial Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells

				that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.
138	HPMDK28	437	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
139	HPRAL78	438	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al.,

				Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
140	HRABA80	439	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
140	HRABA80	439	Activation of Endothelial Cell ERK Signaling Pathway.	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Berra et al., Biochem Pharmacol 60(8):1171-1178 (2000); Gupta et al., Exp Cell Res 247(2):495-504 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-

				500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.
140	HRABA80	439	Upregulation of CD152 and activation of T cells	CD152 FMAT. CD152 (a.k.a. CTLA-4) expression is restricted to activated T cells. CD152 is a negative regulator of T cell proliferation. Reduced CD152 expression has been linked to hyperproliferative and autoimmune diseases. Overexpression of CD152 may lead to impaired immunoresponses. Assays for immunomodulatory proteins important in the maintenance of T cell homeostasis and expressed almost exclusively on CD4+ and CD8+ T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, maintain T cell homeostasis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD152, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); McCoy et al., Immunol Cell Biol 77(1):1-10 (1999); Oostervegal et al., Curr Opin Immunol 11(3):294-300 (1999); and Saito T, Curr Opin Immunol 10(3):313-321 (1998), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
141	HRACD15	440	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the

				invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
141	HRACD15	440	Activation of T-Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit immune cell (e.g. T-cell) proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.
141	HRACD15	440	Regulation of apoptosis of immune cells (such as mast cells).	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate caspase protease-mediated apoptosis in immune cells (such as, for example, in mast cells). Mast cells are found in connective and mucosal tissues throughout the body, and their activation via immunoglobulin E -antigen, promoted by T helper cell type 2 cytokines, is an important component of allergic disease. Dysregulation of mast cell apoptosis may play a role in allergic disease and mast cell tumor survival. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity induced by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Masuda A, et al., J Biol Chem, 276(28):26107-26113 (2001); Yeatman CF 2nd, et al., J Exp Med, 192(8):1093-1103 (2000);Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and

				Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Immune cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary immune cells that may be used according to these assays include mast cells such as the HMC human mast cell line.
142	HRACJ35	441	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
142	HRACJ35	441	Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to meaure the upregulation of cell surface VCAM-1 expresssion in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.
143	HRGBL78	442	Stimulation of	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely

			insulin secretion from pancreatic beta cells.	modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
144	HROAJ39	443	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
145	HROBD68	444	Regulation of	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or

			apoptosis in pancreatic beta cells.	routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
146	HSAWD74	445	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be

				routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
146	HSAWD74	445	Activation of transcription through NFAT response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
147	HSDEK49	446	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.

147	HSDEK49	446	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
148	HSDFJ26	447	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4lle cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.
149	HSDSB09	448	Regulation of transcription via DMEF1 response	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The

			element in adipocytes and pre-adipocytes	DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed inThai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
149	HSDSB09	448	Activation of transcription through cAMP response element (CRE) in pre-adipocytes.	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.

149	HSDSB09	448	Activation of transcription through serum response element in pre-adipocytes.	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
149	HSDSB09	448	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.
149	HSDSB09	448	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the

				invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.
149	HSDSB09	448	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
149	HSDSB09	448	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or

				antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
149	HSDSB09	448	Activation of transcription through NFAT response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
149	HSDSB09	448	Activation of transcription through NFKB response element in immune cells (such as mast	This reporter assay measures activation of the NFkB signaling pathway in HMC-1 human mast cell line. Activation of NFkB in mast cells has been linked to production of certain cytokines, such as IL-6 and IL-9. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity

			cells).	of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Stassen et al, J Immunol 166(7):4391-8 (2001); and Marquardt and Walker, J Allergy Clin Immunol 105(3):500-5 (2000), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
149	HSDSB09	448	Activation of transcription through STAT6 response element in immune cells (such as mast cells).	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element in immune cells (such as in the human HMC-1 mast cell line) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Sherman, Immunol Rev 179:48-56 (2001); Malaviya and Uckun, J Immunol 168:421-426 (2002); Masuda et al., J Biol Chem 275(38):29331-29337 (2000); and Masuda et al., J Biol Chem 276:26107-26113 (2001), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.
149	HSDSB09	448	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995);

				and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
149	HSDSB09	448	Activation of transcription through NFKB response element in immune cells (such as basophils).	This reporter assay measures activation of the NFkB signaling pathway in Ku812 human basophil cell line. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which are herein incorporated by reference in its entirety. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate into mature basophils.
149	HSDSB09	448	Activation of transcription through STAT6 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the SUPT cell line, which

				is a suspension culture of IL-2 and IL-4 responsive T cells.
149	HSDSB09	448	Activation of transcription through serum response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.
150	HSDSE75	449	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
150	HSDSE75	449	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly

				regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.
151	HSIDJ81	450	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
151	HSIDJ81	450	Activation of transcription	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including

			through NFKB response element in neuronal cells (such as SKNMC cells).	antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of neuronal genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Gill JS, et al., Neurobiol Dis, 7(4):448-461 (2000); Tamatani M, et al., J Biol Chem, 274(13):8531-8538 (1999); Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Neuronal cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary neuronal cells that may be used according to these assays include the SKNMC neuronal cell line.
152	HSKDA27	451	Production of GM-CSF	GM-CSF FMAT. GM-CSF is expressed by activated T cells, macrophages, endothelial cells, and fibroblasts. GM-CSF regulates differentiation and proliferation of granulocytes- macrophage progenitors and enhances antimicrobial activity in neutrophils, monocytes and macrophage. Additionally, GM-CSF plays an important role in the differentiation of dendritic cells and monocytes, and increases antigen presentation. GM-CSF is considered to be a proinflammatory cytokine. Assays for immunomodulatory proteins that promote the production of GM-CSF are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and modulate the growth and differentiation of leukocytes. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as GM-CSF, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Ye et al., J Leukoc Biol (58(2):225-233, the contents of each of which are herein incorporated by reference in its entirety. Natural killer cells that may be used according to these assays are publicly available (e.g., through the ATCC) or may be isolated using techniques disclosed herein or otherwise known in the art. Natural killer (NK) cells are large granular lymphocytes that have cytotoxic activity but do bind antigen. NK cells show antibody-independent killing of tumor cells and also recognize antibody bound on target cells, via NK Fc receptors, leading to cell-mediated cytotoxicity.
152	HSKDA27	451	Regulation of apoptosis in pancreatic beta	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in

			cells.	pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
153	HSKGN81	452	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
154	HSNAD72	453	Stimulation of insulin secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or

			from pancreatic beta cells.	antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
155	HSNMC45	454	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
156	HSQFP66	455	Stimulation of insulin secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or

			from pancreatic beta cells.	antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
157	HSRFZ57	456	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
158	HSUBW09	457	Regulation of transcription through the FAS promoter	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is

			element in hepatocytes	regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
158	HSUBW09	457	Upregulation of CD152 and activation of T cells	CD152 FMAT. CD152 (a.k.a. CTLA-4) expression is restricted to activated T cells. CD152 is a negative regulator of T cell proliferation. Reduced CD152 expression has been linked to hyperproliferative and autoimmune diseases. Overexpression of CD152 may lead to impaired immunoresponses. Assays for immunomodulatory proteins important in the maintenance of T cell homeostasis and expressed almost exclusively on CD4+ and CD8+ T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, maintain T cell homeostasis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD152, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); McCoy et al., Immunol Cell Biol 77(1):1-10 (1999); Oostervegal et al., Curr Opin Immunol 11(3):294-300 (1999); and Saito T, Curr Opin Immunol 10(3):313-321 (1998), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
159	HSVBU91	458	Activation of transcription	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including

			through cAMP response element (CRE) in pre-adipocytes.	antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
159	HSVBU91	458	Activation of Hepatocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Rat liver hepatoma cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat liver hepatoma cells that may be used according to these assays include H4lle cells, which are known to respond to glucocorticoids, insulin, or cAMP derivatives.
159	HSVBU91	458	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes.

				Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
159	HSVBU91	458	Activation of transcription through CD28 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.
160	HTAEE28	459	Protection from Endothelial Cell Apoptosis.	Caspase Apoptosis Rescue. Assays for caspase apoptosis rescue are well known in the art and may be used or routinely modified to assess the ability of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to inhibit caspase protease-mediated apoptosis. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis rescue of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Romeo et al., Cardiovasc Res 45(3): 788-794 (2000); Messmer et al., Br J Pharmacol 127(7): 1633-1640 (1999); and J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used

				according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.
160	HTAEE28	459	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
161	HTECC05	460	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly

				available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
162	HTEEB42	461	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
163	HTEFU65	462	Activation of transcription through cAMP response element (CRE) in pre-adipocytes.	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-

				6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.
163	HTEFU65	462	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
163	HTEFU65	462	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al.,"Effect of transforming growth factor

				beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.
163	HTEFU65	462	Production of IFNgamma using a T cells	IFNgamma FMAT. IFNg plays a central role in the immune system and is considered to be a proinflammatory cytokine. IFNg promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFNg), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
163	HTEFU65	462	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li,

				M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
164	HTELP17	463	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4lle cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.
164	HTELP17	463	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely

				generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
165	HTELS08	464	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4lle cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.
166	HTLEP53	465	Endothelial Cell Apoptosis	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Induction of apoptosis in endothelial cells supporting the vasculature of tumors is associated with tumor regression due to loss of tumor blood supply. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.

166	HTLEP53	465	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
167	HTPCS72	466	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995);Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids.

				ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
168	HTPIH83	467	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
169	HTSEW17	468	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable

				insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
169	HTSEW17	468	Activation of transcription through NFKB response element in immune cells (such as B-cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Gri G, et al., Biol Chem, 273(11):6431-6438 (1998); Pyatt DW, et al., Cell Biol Toxicol 2000;16(1):41-51 (2000); Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Immune cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary immune cells that may be used according to these assays include the Reh B-cell line.
170	HTTBI76	469	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
170	HTTBI76	469	Upregulation of CD69 and	CD69 FMAT. CD69 is an activation marker that is expressed on activated T cells, B cells, and NK cells. CD69 is not expressed on resting T cells, B cells, or NK cells. CD69 has been found to be associated with

			activation of T cells	inflammation. Assays for immunomodulatory proteins expressed in T cells, B cells, and leukocytes are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD69, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Ferenczi et al., J Autoimmun 14(1):63-78 (200); Werfel et al., Allergy 52(4):465-469 (1997); Taylor-Fishwick and Siegel, Eur J Immunol 25(12):3215-3221 (1995); and Afetra et al., Ann Rheum Dis 52(6):457-460 (1993), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.
171	HTTBS64	470	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.

172	HTXJM03	471	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.
173	HTXON32	472	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and

				glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.
174	HUFCJ30	473	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
175	HUVEB53	474	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells

				produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.
176	HWAAD63	475	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.
176	HWAAD63	475	Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to meaure the upregulation of cell surface VCAM-1 expresssion in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.
176	HWAAD63	475	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J,

				15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).
177	HWADJ89	476	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.
177	HWADJ89	476	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.
178	HWBFX31	477	Regulation of	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or

			transcription of Malic Enzyme in adipocytes	routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipoocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.

Table 2 further characterizes certain encoded polypeptides of the invention, by providing the results of comparisons to protein and protein family databases. The first column provides a unique clone identifier, "Clone ID NO:", corresponding to a cDNA clone disclosed in Table 1A and/or Table 1B. The second column provides the unique contig identifier, "Contig ID:" which allows correlation with the information in Table 1B. The third column provides the sequence identifier, "SEQ ID NO:", for the contig polynucleotide sequences. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. The fifth column provides a description of the PFAM/NR hit identified by each analysis. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, score/percent identity, provides a quality score or the percent identity, of the hit disclosed in column five. Comparisons were made between polypeptides encoded by polynucleotides of the invention and a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM"), as described below.

The NR database, which comprises the NBRF PIR database, the NCBI GenPept database, and the SIB SwissProt and TrEMBL databases, was made non-redundant using the computer program nrdb2 (Warren Gish, Washington University in Saint Louis). Each of the polynucleotides shown in Table 1B, column 3 (e.g., SEQ ID NO:X or the 'Query' sequence) was used to search against the NR database. The computer program BLASTX was used to compare a 6-frame translation of the Query sequence to the NR database (for information about the BLASTX algorithm please see Altshul et al., J. Mol. Biol. 215:403-410 (1990), and Gish and States, Nat. Genet. 3:266-272 (1993). A description of the sequence that is most similar to the Query sequence (the highest scoring 'Subject') is shown in column five of Table 2 and the database accession number for that sequence is provided in column six. The highest scoring 'Subject' is reported in Table 2 if (a) the estimated probability that the match occurred by chance alone is less than 1.0e-07, and (b) the match was not to a known repetitive element. BLASTX returns alignments of short polypeptide segments of the Query and Subject sequences which share a high degree of similarity; these segments are known as High-Scoring Segment Pairs or HSPs. Table 2 reports the degree of similarity between the Query and the Subject for each HSP as a percent identity in Column 7. The percent identity is determined by dividing the number of exact matches between the two aligned sequences in the HSP, dividing by the number of Query amino acids in the HSP and multiplying by 100. The polynucleotides of SEQ ID NO:X which encode the polypeptide sequence that generates an HSP are delineated by columns 8 and 9 of Table 2.

The PFAM database, PFAM version 2.1, (Sonnhammer, Nucl. Acids Res., 26:320-322, 1998))consists of a series of multiple sequence alignments; one alignment for each protein family. Each multiple sequence alignment is converted into a probability model called a Hidden Markov

Model, or HMM, that represents the position-specific variation among the sequences that make up the multiple sequence alignment (see, e.g., Durbin, et al., *Biological sequence analysis: probabilistic models of proteins and nucleic acids*, Cambridge University Press, 1998 for the theory of HMMs). The program HMMER version 1.8 (Sean Eddy, Washington University in Saint Louis) was used to compare the predicted protein sequence for each Query sequence (SEQ ID NO:Y in Table 1B.1) to each of the HMMs derived from PFAM version 2.1. A HMM derived from PFAM version 2.1 was said to be a significant match to a polypeptide of the invention if the score returned by HMMER 1.8 was greater than 0.8 times the HMMER 1.8 score obtained with the most distantly related known member of that protein family. The description of the PFAM family which shares a significant match with a polypeptide of the invention is listed in column 5 of Table 2, and the database accession number of the PFAM hit is provided in column 6. Column 7 provides the score returned by HMMER version 1.8 for the alignment. Columns 8 and 9 delineate the polynucleotides of SEQ ID NO:X which encode the polypeptide sequence which show a significant match to a PFAM protein family.

As mentioned, columns 8 and 9 in Table 2, "NT From" and "NT To", delineate the polynucleotides of "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth column. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the polynucleotides of SEQ ID NO:X delineated in columns 8 and 9 of Table 2. Also provided are polynucleotides encoding such proteins, and the complementary strand thereto.

The nucleotide sequence SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, the nucleotide sequences of SEQ ID NO:X are useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in ATCC Deposit No:Z. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to these polypeptides, or fragments thereof, and/or to the polypeptides encoded by the cDNA clones identified in, for example, Table 1A and/or 1B.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA

sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and a predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing cDNA ATCC Deposit No:Z (e.g., as set forth in columns 2 and 3 of Table 1A and/or as set forth, for example, in Table 1B, 6, and 7). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

Table 2

cDNA Clone ID	Contig ID:	SEQ ID NO: X	Analysis Method	PFam/NR Description	PFam/NR Accession Number	Score/ Percent Identity	NT From	NT To
H2CBU83	884134	11	WUblastx.64	(Q9NYD1) G-PROTEIN-COUPLED RECEPTOR 48.	Q9NYD1	100%	10	777
HACBD91	637482	13	WUblastx.64	NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) chain NDUFB4 - human	pir|JE0383|JE0383	100% 95%	211 1306	357 1368
HAGAQ26	561996	14	WUblastx.64	(Q9UKG4) NA+/SULFATE COTRANSPORTER SUT-1.	Q9UKG4	99% 93%	414 2	1001 433
HAJAN23	872551	191	HMMER 2.1.1	PFAM: Carboxyl transferase domain	PF01039	126.6	294	617
			WUblastx.64	(Q9HCC0) NON-BIOTIN CONTAINING SUBUNIT OF 3-METHYLCROTONYL-COA CARBOX	Q9HCC0	91% 93%	120 557	665 1807
HAJBR69	638516	17	WUblastx.64	(Q9JIG5) UBIQUITIN SPECIFIC PROTEASE (FRAGMENT).	Q9JIG5	69%	677	48
HAMFE15	905695	18	HMMER 2.1.1	PFAM: Diacylglycerol kinase catalytic domain (presumed)	PF00781	22.9	1807	1956
			WUblastx.64	(Q9NP48) PUTATIVE LIPID KINASE (CDNA FLJ10842 FIS, CLONE NT2RP4001343	Q9NP48	93%	1495	2757
HAMFE15	823350	192	blastx.2	PUTATIVE LIPID KINASE (CDNA FLJ10842 FIS, CLONE NT2RP4001343).	sp|Q9NP48|Q9NP48	93%	1503	2756
HAMGR28	892971	19	WUblastx.64	(AAH07438) Similar to RIKEN cDNA 2610511E22 gene.	AAH07438	100%	59	823
HAPOM49	769555	20	WUblastx.64	(Q9BZM1) GROUP XII SECRETED PHOSPHOLIPASE A2.	Q9BZM1	99%	251	817
HATBR65	635514	21	WUblastx.64	(Q9H728) CDNA: FLJ21463 FIS, CLONE COL04765.	Q9H728	70% 68%	750 801	610 754
HAUAI83	639009	22	WUblastx.	(BAB27250) 13 days embryo liver cDNA, RIKEN full-le	BAB27250	88%	160	399

			64			90% 100%	25 489	84 557
HAUAI83	383592	195	blastx.2	(AF059620) My006 protein [Homo sapiens]	gb|AAG431 19.1|AF059 620_1	100%	406	723
HBGBA69	709658	196	WUblastx. 64	(AAH17488) Hypothetical 22.4 kDa protein (Fragment)	AAH17488	78% 100%	158 211	226 780
HBIAE26	514418	25	WUblastx. 64	(AAK55521) PRO0764.	AAK55521	83% 65%	1009 983	974 744
HBINS58	1352386	26	blastx.14	(Q9D6W7) 2310047N01RIK PROTEIN.	Q9D6W7	82% 64%	255 177	578 251
HBINS58	961712	197	WUblastx. 64	(Q9D6W7) 2310047N01RIK PROTEIN.	Q9D6W7	78%	191	589
HBINS58	892924	198	blastx.2	(AF106518) sialomucin CD164 [Homo sapiens]	gb|AAC824 73.1|	33%	241	576
HCE2F54	634016	28	HMMER 2.1.1	PFAM: Histone-like transcription factor (CBF/NF-Y) and archaeal histone	PF00808	19	868	1005
			WUblastx. 64	(AAH07642) Unknown (protein for IMAGE:3534358) (Fra	AAH07642	99%	298	1122
HCE3G69	728432	29	WUblastx. 64	(Q9H0K7) HYPOTHETICAL 12.4 KDA PROTEIN (UNKNOWN) (PROTEIN FOR MGC:303	Q9H0K7	100%	1294	1647
HCE3G69	494346	199	blastx.2	(AL136758) hypothetical protein [Homo sapiens]	emb|CAB66 692.1|	100%	1295	1648
HCE5F43	612796	30	WUblastx. 64	(Q9H8M7) CDNA FLJ13397 FIS, CLONE PLACE1001351.	Q9H8M7	100% 100%	9 56	53 928
HCEFB80	1143407	31	WUblastx. 64	(Q96FR3) Unknown (protein for MGC:18083).	Q96FR3	81%	1785	1979
HCEWE20	543370	32	WUblastx. 64	(Q9P1J1) PRO1546.	Q9P1J1	76% 79%	501 601	551 717
HCGMD59	636078	33	WUblastx. 64	catalase (EC 1.11.1.6) - Campylobacter jejuni	pir|I40767|I 40767	97%	296	186
HCNSM70	637547	35	HMMER 2.1.1	PFAM: Immunoglobulin domain	PF00047	32	224	481

			WUblastx.64	(O60487) EPITHELIAL V-LIKE ANTIGEN PRECURSOR (EPITHELIAL V-LIKE ANTIG	O60487	94%	107	751
HCNSM70	589445	203	WUblastx.64	(O60487) EPITHELIAL V-LIKE ANTIGEN PRECURSOR (EPITHELIAL V-LIKE ANTIG	O60487	100% 99%	161 408	409 806
HCWDS72	707833	37	WUblastx.64	conserved hypothetical protein PA1527 [imported] - Pseudomonas aeruginosa (strain PAO1)	pir|D83454|D83454	77%	318	4
HCWKC15	553621	38	WUblastx.64	(Q9NX85) CDNA FLJ20378 FIS, CLONE KAIA0536.	Q9NX85	77% 56% 63%	538 710 708	419 663 532
HDHEB60	499233	39	WUblastx.64	(Q9Y5Y5) PEROXISOMAL BIOGENESIS FACTOR 16.	Q9Y5Y5	81%	277	1284
HDPBA28	1062783	40	WUblastx.64	(Q9UKY2) ADIPOCYTE-DERIVED LEUCINE AMINOPEPTIDASE.	Q9UKY2	94%	259	3081
HDPBA28	866429	204	HMMER 2.1.1	PFAM: Peptidase family M1	PF01433	613.6	228	1391
			WUblastx.64	(Q9UKY2) ADIPOCYTE-DERIVED LEUCINE AMINOPEPTIDASE.	Q9UKY2	99%	69	2891
HDPCL63	1019008	41	WUblastx.64	(Q9Y519) HYPOTHETICAL 42.3 KDA PROTEIN.	Q9Y519	99%	14	835
HDPCL63	847045	205	WUblastx.64	(Q9Y519) HYPOTHETICAL 42.3 KDA PROTEIN.	Q9Y519	97%	2	730
HDPGT01	771583	44	WUblastx.64	(Q9Y2B3) LCAT-LIKE PROTEIN (LLPL).	Q9Y2B3	100% 100%	8 264	262 1244
HDPJM30	879325	46	WUblastx.64	(O94759) LONG TRANSIENT RECEPTOR POTENTIAL CHANNEL 2 (LTRPC	TRL2_HUMAN	99%	17	1633
HDPJM30	603517	207	WUblastx.64	(O94759) LONG TRANSIENT RECEPTOR POTENTIAL CHANNEL 2 (LTRPC	TRL2_HUMAN	89% 96% 98%	416 378 1	1312 530 378
HDPMM88	972734	47	HMMER 2.1.1	PFAM: E1-E2 ATPase	PF00122	31	475	543
			WUblastx.64	(P98198) POTENTIAL PHOSPHOLIPID-TRANSPORTING ATPASE ID (EC	AT1D_HUMAN	66% 32%	106 2917	2907 2991
HDPMM88	906121	208	blastx.2	(AF038007) FIC1 [Homo sapiens]	gb|AAC634	62%	3	467

					61.1|			
HDPMM88	874074	211	blastx.2	(AF038007) FIC1 [Homo sapiens]	gb|AAC634 61.1|	56%	1023	13
HDPOJ08	731863	48	WUblastx. 64	(Q9H7X1) CDNA FLJ14153 FIS, CLONE NT2RM1000092, WEAKLY SIMILAR TO MUL	Q9H7X1	84% 30% 99%	524 315 12	904 479 524
HDPPN86	1037893	49	WUblastx. 64	(Q9BVN4) HYPOTHETICAL 59.4 KDA PROTEIN.	Q9BVN4	77% 100% 97% 47% 98%	5063 919 1942 4983 4611	5194 1308 2175 5045 4799
HDPSB18	1043263	50	WUblastx. 64	(Q9H5R3) CDNA: FLJ23147 FIS, CLONE LNG09295.	Q9H5R3	70%	3363	3163
HDPSH53	1309174	51	WUblastx. 64	(Q9H257) CASPASE RECRUITMENT DOMAIN PROTEIN 9.	Q9H257	79% 100%	1011 262	1184 426
HDPSH53	1040056	218	WUblastx. 64	(Q9H257) CASPASE RECRUITMENT DOMAIN PROTEIN 9.	Q9H257	100% 65% 92%	1131 1010 301	1184 1114 423
HDPSP01	689129	220	WUblastx. 64	(Q9BR97) UNKNOWN (PROTEIN FOR MGC:10763).	Q9BR97	90% 98% 100%	227 1078 1664	1114 1668 1744
HDPUW68	812737	54	HMMER 2.1.1	PFAM: Immunoglobulin domain	PF00047	38.9	844	1005
			WUblastx. 64	(Q9Y286) QA79 MEMBRANE PROTEIN, ALLELIC VARIANT AIRM-1B PRECURSOR.	Q9Y286	95%	70	1440
HDPXY01	879048	55	WUblastx. 64	hypothetical protein DKFZp434A139.1 - human (fragments)	pir|T43490| T43490	50% 83%	637 3	678 620
HDTBD53	972757	56	WUblastx. 64	(Q9BTV4) UNKNOWN (PROTEIN FOR MGC:3222).	Q9BTV4	100%	183	1382
HDTBV77	785879	57	WUblastx. 64	(Q9BT94) UNKNOWN (PROTEIN FOR MGC:10848).	Q9BT94	99% 69%	65 2131	2137 2169
HDTDQ23	1306984	58	WUblastx. 64	calcium-binding protein (clone pMP41) - mouse (fragment)	pir|S04970|S 04970	100%	1611	1709

HDTDQ23	879009	226	WUblastx.64	calcium-binding protein (clone pMP41) - mouse (fragment)	pir|S04970|S04970	100%	1623	1721
HE2DE47	619852	59	WUblastx.64	(Q9NZN8) NOT2P (CCR4-NOT TRANSCRIPTION COMPLEX, SUBUNIT 2).	Q9NZN8	96%	808	2427
HE2NV57	740750	60	WUblastx.64	(Q9UGV6) BK445C9.3 (HIGH-MOBILITY GROUP (NONHISTONE CHROMOSOMAL) PROT	Q9UGV6	31% 66%	321 71	866 106
HE2PH36	570903	61	WUblastx.64	(AAH07609) Similar to hypothetical protein PRO1722.	AAH07609	56% 90% 68%	1359 1524 1484	1285 1492 1553
HE8DS15	847060	62	WUblastx.64	(Q9WVT0) SEVEN TRANSMEMBRANE RECEPTOR.	Q9WVT0	80% 24% 87%	1 48 269	270 146 985
HEOMQ63	603533	64	WUblastx.64	(Q9BQM3) DJ842G6.1.1 (NOVEL PROTEIN) (FRAGMENT).	Q9BQM3	100% 100% 99%	1036 592 635	1293 639 937
HFABH95	566712	66	WUblastx.64	(Q9QZH5) PUTATIVE PHOSPHATE/PHOSPHOENOLPYRUVATE TRANSLOCATOR.	Q9QZH5	88% 65%	513 9	944 77
HFAEF57	534142	67	WUblastx.64	(Q9HBN2) HYPOTHETICAL 15.8 KDA PROTEIN.	Q9HBN2	47%	601	425
HFCEB37	411345	68	WUblastx.64	(Q9NYC6) NEURONAL SPECIFIC TRANSCRIPTION FACTOR DAT1.	Q9NYC6	94%	4	204
HFGAD82	513669	70	WUblastx.64	membrane glycoprotein M6 - mouse	pir|I78556|I78556	92%	249	410
HFIUR10	532060	71	WUblastx.64	(AAK55521) PRO0764.	AAK55521	47% 75%	369 497	307 411
HFTBM50	545012	72	WUblastx.64	(Q9H8P0) CDNA FLJ13352 FIS, CLONE OVARC1002165, WEAKLY SIMILAR TO 3-O	Q9H8P0	100% 91%	23 198	229 524
HFXJX44	701988	75	WUblastx.64	(Q9N083) UNNAMED PORTEIN PRODUCT.	Q9N083	57%	1378	1082
HFXKT05	658690	76	WUblastx.64	(Q9H5H7) CDNA: FLJ23425 FIS, CLONE HEP22862.	Q9H5H7	81%	5	1015
HGBHI35	570262	77	HMMER	PFAM: Enoyl-CoA hydratase/isomerase family	PF00378	184.6	213	722

			2.1.1					
			WUblastx. 64	(Q9DBD3) 1300017C12RIK PROTEIN.	Q9DBD3	90%	225	962
HHGCM76	662329	81	WUblastx. 64	(Q96FV2) Unknown (protein for IMAGE:3945715) (Fragment).	Q96FV2	94% 98%	7 378	114 536
HHGCM76	383547	230	WUblastx. 64	(Q96FV2) Unknown (protein for IMAGE:3945715) (Fragment).	Q96FV2	94% 98%	7 378	114 536
HHPEN62	695134	82	HMMER 2.1.1	PFAM: Peptidase family M20/M25/M40	PF01546	148.9	510	1535
			WUblastx. 64	(Q96KN2) Glutamate carboxypeptidase-like protein 2.	Q96KN2	99%	183	1706
HJABB94	456466	83	WUblastx. 64	(Q9BWV3) PROTEIN KINASE NYD-SP15.	Q9BWV3	100% 38% 94%	8 1127 1227	250 1192 1523
HJACG30	895505	84	WUblastx. 64	(Q9UM21) UDP-GLCNAC:A-1,3-D-MANNOSIDE B-1,4-N-ACETYLGLUCOSAMINYLTRANS	Q9UM21	96%	291	389
HJBCY35	719729	85	WUblastx. 64	hypothetical protein DKFZp586J0619.1 - human (fragment)	pir|T08758| T08758	100%	1	1212
HJPAD75	651337	86	WUblastx. 64	(Q9H5F8) CDNA: FLJ23476 FIS, CLONE HSI14935.	Q9H5F8	98%	8	232
HKABZ65	862030	87	WUblastx. 64	(Q96LB9) Peptidoglycan recognition protein-I-alpha precursor.	Q96LB9	90% 39%	77 137	802 541
HKABZ65	665424	233	WUblastx. 64	(Q96LB9) Peptidoglycan recognition protein-I-alpha precursor.	Q96LB9	99% 45%	69 129	794 533
HKACB56	554616	88	HMMER 2.1.1	PFAM: Kazal-type serine protease inhibitor domain	PF00050	76.3	114	266
			WUblastx. 64	(P01001) ACROSIN INHIBITORS IIA AND IIB (BUSI-II).	IAC2_BOVIN	82%	96	266
HKACD58	552465	234	WUblastx. 64	(Q96BH2) Hypothetical 34.4 kDa protein.	Q96BH2	86% 87%	795 122	1208 724
HKAEV06	638238	235	WUblastx. 64	(Q9NVA4) CDNA FLJ10846 FIS, CLONE NT2RP4001373.	Q9NVA4	96% 100% 96%	367 197 480	459 367 1541

HKAFT66	946512	91	WUblastx. 64	(Q9CPS2) 4933428I03RIK PROTEIN.	Q9CPS2	72% 62% 84%	29 82 274	61 231 828
HKAFT66	889258	236	blastx	(AF022985) No definition line found [Caenorhabditis elegans]	gb|AAB699 75.1|	21% 25% 29%	292 562 691	543 702 801
HKAFT66	904790	237	blastx.2	(AJ271091) B-ind1 protein [Homo sapiens]	emb|CAB69 070.1|	34% 45%	12 298	296 516
HKB1E57	876571	92	HMMER 2.1.1	PFAM: Uncharacterized protein family UPF0004	PF00919	320.5	178	843
			WUblastx. 64	(Q9BWZ5) DJ1187J4.4 (CGI-05 PROTEIN (LOC51654) SIMILAR TO RAT CDK5 AC	Q9BWZ5	99%	1	879
HKB1E57	654871	238	WUblastx. 64	(Q9BVG6) SIMILAR TO CGI-05 PROTEIN.	Q9BVG6	90%	78	167
HKFBC53	701893	239	WUblastx. 64	hypothetical protein F16H11.1 - Caenorhabditis elegans	pir|T16084| T16084	45% 59% 50% 37% 37%	132 11 82 566 293	305 106 129 673 1366
HKFBC53	513190	240	WUblastx. 64	hypothetical protein F16H11.1 - Caenorhabditis elegans	pir|T16084| T16084	35%	135	902
HKFBC53	383426	241	WUblastx. 64	hypothetical protein F16H11.1 - Caenorhabditis elegans	pir|T16084| T16084	38% 32%	704 135	949 713
HKGDL36	877489	94	WUblastx. 64	(Q9UHG2) PROSAAS PRECURSOR (GRANIN-LIKE NEUROENDOCRINE PEPTIDE PRECUR	Q9UHG2	100% 63%	563 53	793 409
HKGDL36	704088	242	WUblastx. 64	(Q9UHG2) PROSAAS PRECURSOR (GRANIN-LIKE NEUROENDOCRINE PEPTIDE PRECUR	Q9UHG2	82% 49%	99 55	830 555
HKISB57	625956	95	WUblastx. 64	(AAL36150) Smoothelin-B3.	AAL36150	28% 100% 98% 27% 26% 44%	262 201 1107 271 532 954	582 1013 1256 480 966 1052

HKMLM11	514788	96	WUblastx. 64	(Q9P059) HSPC323 (FRAGMENT).	Q9P059	71% 85%	332 148	562 462
HKMMW74	581399	97	WUblastx. 64	(AAG23169) HC6.	AAG23169	73%	1784	1662
HLDQR62	753742	99	WUblastx. 64	(Q9NQW2) PROGRESSIVE ANKYLOSIS-LIKE PROTEIN.	Q9NQW2	100% 99%	41 376	382 1002
HLDQU79	740755	100	WUblastx. 64	(O75477) KE04P.	O75477	100%	105	1142
HLICQ90	791828	103	WUblastx. 64	(Q96N65) CDNA FLJ31349 fis, clone MESAN2000092, moderately similar to	Q96N65	95% 93%	571 59	636 616
HLTHR66	699812	104	HMMER 2.1.1	PFAM: PAP2 superfamily	PF01569	22.3	35	151
			WUblastx. 64	(Q9D4F2) 4932443D16RIK PROTEIN.	Q9D4F2	93%	2	229
HLTIP94	1087335	105	WUblastx. 64	(Q96DH6) Hypothetical 35.2 kDa protein.	Q96DH6	80%	579	740
HLTIP94	1047690	244	HMMER 2.1.1	PFAM: RNA recognition motif. (a.k.a. RRM, RBD, or RNP domain)	PF00076	143.1	40	-172
HLWAA17	629552	106	WUblastx. 64	(Q9NY26) IRT1 PROTEIN (SIMILAR TO ZINC/IRON REGULATED TRANSPORTER-LIK	Q9NY26	99%	85	960
HMADK33	561941	108	WUblastx. 64	hypothetical protein DKFZp761P2414.1 - human	pir|T47139| T47139	100% 87% 96%	152 394 237	175 417 395
HMAMI15	1352406	109	blastx.14	(Q96QY4) BA134O15.1 (similar to citrate lyase) (Fragment).	Q96QY4	99%	85	1023
HMAMI15	1049263	245	WUblastx. 64	(Q96QY4) BA134O15.1 (similar to citrate lyase) (Fragment).	Q96QY4	79% 100%	372 84	920 440
HMCFY13	635301	110	WUblastx. 64	(AAL32175) Chromosome 17 open reading frame 26.	AAL32175	95%	36	737
HMEED18	560775	112	WUblastx. 64	(Q9H651) CDNA: FLJ22604 FIS, CLONE HSI04630 (BBP-LIKE PROTEIN 2).	Q9H651	93%	34	696
HMSDL37	973996	115	WUblastx. 64	(Q9H743) CDNA: FLJ21394 FIS, CLONE COL03536.	Q9H743	66%	1189	1497
HMSFI26	560229	116	WUblastx.	(Q14713) POT. ORF V.	Q14713	57%	1075	1019

			64			39%	1041	805
HMVBS81	639203	117	WUblastx. 64	(O95070) 54TMP.	O95070	100%	10	450
HMWFT65	562063	119	WUblastx. 64	(Q96AZ2) Similar to hypothetical protein FLJ21463.	Q96AZ2	67%	1342	1205
HNFFC43	753337	121	WUblastx. 64	(Q96BY8) Hypothetical 55.2 kDa protein.	Q96BY8	97% 66% 87% 99%	319 428 651 903	453 769 839 1517
HNFIY77	634551	122	WUblastx. 64	(AAL47020) KCCR13L.	AAL47020	96% 99%	866 105	1030 866
HNFJF07	577013	123	WUblastx. 64	(AAL55831) Hypothetical 14.1 kDa protein.	AAL55831	65%	585	457
HNGIJ31	519120	125	WUblastx. 64	(Q9N083) UNNAMED PORTEIN PRODUCT.	Q9N083	73% 54% 66%	566 615 454	610 725 561
HNGJE50	561568	126	WUblastx. 64	(Q9HBS7) HYPOTHETICAL 14.2 KDA PROTEIN.	Q9HBS7	64% 62%	1028 919	945 734
HNHEU93	634851	129	WUblastx. 64	(Q9H387) PRO2550.	Q9H387	67%	741	418
HNHFM14	664507	130	WUblastx. 64	(Q9N8S9) POSSIBLE (HHV-6) U1102, VARIANT A DNA, COMPLETE VIRION GENOM	Q9N8S9	74% 45% 63% 79% 76%	6 17 11 9 9	122 223 124 110 122
HNHNB29	895462	131	WUblastx. 64	(Q9P195) PRO1722.	Q9P195	79% 75%	1543 1398	1674 1553
HNHOD46	843488	132	WUblastx. 64	(O60448) NEURONAL THREAD PROTEIN AD7C-NTP.	O60448	76% 56% 56% 52% 73% 59%	334 646 645 844 331 353	552 921 713 894 498 625

						50% 70% 48% 50% 35% 31% 50% 61%	828 721 781 558 401 283 379 486	917 792 915 791 595 552 462 839
HNTBI26	1310821	133	WUblastx. 64	(Q96F65) Similar to RIKEN cDNA 0610031J06 gene (Fragment).	Q96F65	92% 60%	145 7	987 150
HNTBI26	796807	251	WUblastx. 64	(Q96F65) Similar to RIKEN cDNA 0610031J06 gene (Fragment).	Q96F65	94% 97% 29% 95%	516 149 1096 11	992 544 1206 154
HNTBL27	545534	134	WUblastx. 64	(Q96AA3) Putative endoplasmic reticulum multispan transmembrane prote	Q96AA3	98% 33% 40% 96%	243 13 646 13	500 168 711 261
HNTCE26	1160395	135	HMMER 2.1.1	PFAM: 7 transmembrane receptor (rhodopsin family)	PF00001	137.5	282	1037
			WUblastx. 64	(Q9H1Y3) DJ317G22.2 (ENCEPHALOPSIN) (PANOPSIN).	Q9H1Y3	100%	111	1316
HNTCE26	853373	253	HMMER 2.1.1	PFAM: 7 transmembrane receptor (rhodopsin family)	PF00001	23.2	63	218
			WUblastx. 64	(Q9H1Y3) DJ317G22.2 (ENCEPHALOPSIN) (PANOPSIN).	Q9H1Y3	95% 100%	370 12	495 377
HODDN92	422913	138	WUblastx. 64	(Q9H1S5) BA110H4.2 (SIMILAR TO MEMBRANE PROTEIN).	Q9H1S5	100%	1119	1021
HOFMQ33	1184465	139	WUblastx. 64	(O15232) MATRILIN-3 PRECURSOR.	MTN3_HUMAN	85%	205	1500
HOFMQ33	919896	255	HMMER 2.1.1	PFAM: von Willebrand factor type A domain	PF00092	189.8	288	815
			WUblastx.	(O15232) MATRILIN-3 PRECURSOR.	MTN3_HU	85%	204	1499

			64		MAN			
HOFMQ33	906694	256	HMMER 2.1.1	PFAM: von Willebrand factor type A domain	PF00092	162.2	318	737
HOFOC73	931871	140	HMMER 2.1.1	PFAM: Papain family cysteine protease	PF00112	22.3	192	311
			WUblastx. 64	(BAB22302) Adult male kidney cDNA, RIKEN full-lengt	BAB22302	71% 87%	72 316	341 918
HOQBJ82	858338	262	WUblastx. 64	(CAC37795) H-l(3)mbt-like protein.	CAC37795	66% 57%	436 41	585 496
HOQBJ82	857453	263	HMMER 2.1.1	PFAM: SET domain	PF00856	211.5	100	489
HOSDJ25	854234	143	WUblastx. 64	(Q9D8Y9) 1810018L05RIK PROTEIN.	Q9D8Y9	85% 86%	468 143	593 544
HPEAD79	520202	144	WUblastx. 64	(Q96NR6) CDNA FLJ30278 fis, clone BRACE2002755.	Q96NR6	48%	498	806
HPIBO15	1310868	145	WUblastx. 64	(Q9CQS3) 1110018M03RIK PROTEIN.	Q9CQS3	93%	128	757
HPIBO15	590741	265	WUblastx. 64	(Q9CQS3) 1110018M03RIK PROTEIN.	Q9CQS3	88% 95% 97%	127 507 401	402 722 508
HPJBI33	685699	146	WUblastx. 64	(O60448) NEURONAL THREAD PROTEIN AD7C-NTP.	O60448	49% 33% 51% 35% 33% 51% 59% 52% 34% 50% 47%	617 633 24 570 1317 155 154 137 41 3 886	934 890 122 872 1415 256 234 256 256 146 942
HPMDK28	846357	148	WUblastx. 64	(Q9NP77) CDNA FLJ10947 FIS, CLONE PLACE1000066, WEAKLY SIMILAR TO SSU	Q9NP77	100%	163	666

HPMDK28	639118	269	WUblastx.64	(Q9NP77) CDNA FLJ10947 FIS, CLONE PLACE1000066, WEAKLY SIMILAR TO SSU	Q9NP77	100%	157	660
HPRAL78	844216	270	WUblastx.64	(AAH08720) Unknown (protein for MGC:8447).	AAH08720	83% 51%	70 490	1017 1068
HPRAL78	484735	271	WUblastx.64	(Q91XD7) Unknown (protein for MGC:18896).	Q91XD7	95%	124	336
HRABA80	882176	150	WUblastx.64	(Q9HA75) CDNA FLJ12122 FIS, CLONE MAMMA1000129.	Q9HA75	63% 68%	221 325	310 459
HRABA80	588460	272	WUblastx.64	(Q9HA75) CDNA FLJ12122 FIS, CLONE MAMMA1000129.	Q9HA75	63% 48% 92%	633 130 233	665 357 493
HRACD15	871221	151	WUblastx.64	(AAH08084) Hypothetical 50.4 kDa protein.	AAH08084	98%	1452	253
HRACJ35	877666	152	WUblastx.64	(Q9Y5X6) BLOOD PLASMA GLUTAMATE CARBOXYPEPTIDASE PRECURSOR (EC 3.4.17	Q9Y5X6	65% 99%	1519 132	1755 1472
HRACJ35	730504	274	WUblastx.64	(Q9Y5X6) BLOOD PLASMA GLUTAMATE CARBOXYPEPTIDASE PRECURSOR (EC 3.4.17	Q9Y5X6	98% 99%	1435 99	1722 1439
HRACJ35	470546	275	blastx.2	AMINOPEPTIDASE.	sp|Q9Y646| Q9Y646	100% 96%	1 507	519 785
HRGBL78	910133	153	HMMER 2.1.1	PFAM: Immunoglobulin domain	PF00047	32	582	755
			WUblastx.64	(AAL58111) FREB.	AAL58111	87%	9	1085
HROAJ39	1181699	154	WUblastx.64	(Q96ES0) Unknown (protein for MGC:16944).	Q96ES0	92%	7	1146
HROBD68	827306	155	WUblastx.64	(Q9H728) CDNA: FLJ21463 FIS, CLONE COL04765.	Q9H728	66% 78%	418 581	576 748
HSAWD74	460527	156	WUblastx.64	(Q9NX85) CDNA FLJ20378 FIS, CLONE KAIA0536.	Q9NX85	67%	967	674
HSDEK49	625998	282	HMMER 2.1.1	PFAM: Immunoglobulin domain	PF00047	18.7	225	470
			WUblastx.64	(Q9Y279) Z39IG PROTEIN PRECURSOR.	Q9Y279	88% 99%	444 126	1040 542

HSDFJ26	834619	158	WUblastx.64	(Q9BYJ0) KSP37.	Q9BYJ0	99%	99	767
HSDFJ26	836071	283	blastx.2	(AB021123) Ksp37 [Homo sapiens]	dbj|BAB39770.1|	83% 77%	238 99	768 281
HSDSE75	545057	160	WUblastx.64	(O60245) PCDH7 (BH-PCDH)A.	O60245	100%	10	702
HSIDJ81	589447	161	WUblastx.64	(Q9H728) CDNA: FLJ21463 FIS, CLONE COL04765.	Q9H728	74%	1289	996
HSKDA27	1074734	285	WUblastx.64	(Q9CRM1) 2610001E17RIK PROTEIN (FRAGMENT).	Q9CRM1	70% 60% 23%	793 1686 1604	1701 1784 1741
HSKDA27	872570	286	blastx.2	(AK020169) putative [Mus musculus]	dbj|BAB32018.1|	47%	666	1562
HSKGN81	676075	163	WUblastx.64	(Q9CZY7) 2610307O08RIK PROTEIN.	Q9CZY7	68%	146	1126
HSNAD72	467397	164	WUblastx.64	(Q9P195) PRO1722.	Q9P195	62% 53% 59%	825 623 730	730 579 536
HSUBW09	413246	168	WUblastx.64	(Q95LL0) Hypothetical 11.3 kDa protein.	Q95LL0	73% 77%	589 327	633 611
HSVBU91	596868	169	WUblastx.64	cytoplasmic linker protein CLIP-115 - rat	pir|T42734|T42734	85%	356	171
HTAEE28	1018291	170	WUblastx.64	(Q9D4I2) 4932408F18RIK PROTEIN.	Q9D4I2	72%	319	1161
HTEEB42	206980	172	HMMER 2.1.1	PFAM: Immunoglobulin domain	PF00047	48.5	500	706
			WUblastx.64	(AAG49022) Junctional adhesion molecule 2.	AAG49022	94%	110	952
HTELP17	836072	174	WUblastx.64	(AAH20029) Hypothetical 39.4 kDa protein.	AAH20029	81%	22	528
HTELS08	847090	175	WUblastx.64	(Q9JI83) EPCS26 (PLAC1) (PLACENTAL SPECIFIC PROTEIN 1).	Q9JI83	34%	33	395
HTLEP53	634852	176	WUblastx.	(Q9H728) CDNA: FLJ21463 FIS, CLONE COL04765.	Q9H728	69%	806	501

			64					
HTPCS72	854941	177	WUblastx.64	(O95880) UNKNOWN.	O95880	100%	2191	2577
HTPCS72	566683	293	WUblastx.64	(O95880) UNKNOWN.	O95880	100%	356	742
HTPIH83	919916	178	HMMER 2.1.1	PFAM: PMP-22/EMP/MP20/Claudin family	PF00822	81.5	127	660
			WUblastx.64	(P57739) CLAUDIN-2.	CLD2_HUMAN	85%	199	807
HTPIH83	895024	294	HMMER 2.1.1	PFAM: PMP-22/EMP/MP20/Claudin family	PF00822	55.9	120	500
			WUblastx.64	(P57739) CLAUDIN-2.	CLD2_HUMAN	87%	192	530
HTTBS64	1008159	181	WUblastx.64	reverse transcriptase-related protein - rabbit (fragment)	pir|S22049|S22049	70% 52%	996 896	895 714
HTXJM03	603918	182	WUblastx.64	(Q9BRH0) SIMILAR TO DKFZP727C091 PROTEIN.	Q9BRH0	100% 99%	470 564	565 1760
HTXON32	838288	183	WUblastx.64	(Q96NR6) CDNA FLJ30278 fis, clone BRACE2002755.	Q96NR6	58% 64%	1397 1194	1498 1397
HWAAD63	838626	186	HMMER 2.1.1	PFAM: Sodium/calcium exchanger protein	PF01699	62.8	346	453
			WUblastx.64	(Q9HC58) SODIUM/CALCIUM EXCHANGER NCKX3.	Q9HC58	65%	229	813
HWAAD63	833089	298	HMMER 2.1.1	PFAM: Sodium/calcium exchanger protein	PF01699	37.8	346	453
			blastx.2	(AF177984) potassium-dependent sodium-calcium exchanger NCKX1 [Gallus gallus]	gb|AAF25808.1|AF177984_1	45% 41% 45% 31%	217 533 453 319	453 793 596 453
HWAAD63	793875	299	HMMER 2.1.1	PFAM: Sodium/calcium exchanger protein	PF01699	113.7	336	773
			blastx.2	(AF025664) Na-Ca+K exchanger [Bos taurus]	gb|AAB88884.1|	43%	207	785

HWBFX31	799427	188	WUblastx.64	(Q9N083) UNNAMED PORTEIN PRODUCT.	Q9N083	56%	1663	1517

RACE Protocol For Recovery of Full-Length Genes

Partial cDNA clones can be made full-length by utilizing the rapid amplification of cDNA ends (RACE) procedure described in Frohman, M.A., et al., Proc. Nat'l. Acad. Sci. USA, 85:8998-9002 (1988). A cDNA clone missing either the 5' or 3' end can be reconstructed to include the absent base pairs extending to the translational start or stop codon, respectively. In some cases, cDNAs are missing the start codon of translation, therefor. The following briefly describes a modification of this original 5' RACE procedure. Poly A+ or total RNA is reverse transcribed with Superscript II (Gibco/BRL) and an antisense or complementary primer specific to the cDNA sequence. The primer is removed from the reaction with a Microcon Concentrator (Amicon). The first-strand cDNA is then tailed with dATP and terminal deoxynucleotide transferase (Gibco/BRL). Thus, an anchor sequence is produced which is needed for PCR amplification. The second strand is synthesized from the dA-tail in PCR buffer, Taq DNA polymerase (Perkin-Elmer Cetus), an oligo-dT primer containing three adjacent restriction sites (XhoI, SalI and ClaI) at the 5' end and a primer containing just these restriction sites. This double-stranded cDNA is PCR amplified for 40 cycles with the same primers as well as a nested cDNA-specific antisense primer. The PCR products are size-separated on an ethidium bromide-agarose gel and the region of gel containing cDNA products the predicted size of missing protein-coding DNA is removed. cDNA is purified from the agarose with the Magic PCR Prep kit (Promega), restriction digested with XhoI or SalI, and ligated to a plasmid such as pBluescript SKII (Stratagene) at XhoI and EcoRV sites. This DNA is transformed into bacteria and the plasmid clones sequenced to identify the correct protein-coding inserts. Correct 5' ends are confirmed by comparing this sequence with the putatively identified homologue and overlap with the partial cDNA clone. Similar methods known in the art and/or commercial kits are used to amplify and recover 3' ends.

Several quality-controlled kits are commercially available for purchase. Similar reagents and methods to those above are supplied in kit form from Gibco/BRL for both 5' and 3' RACE for recovery of full length genes. A second kit is available from Clontech which is a modification of a related technique, SLIC (single-stranded ligation to single-stranded cDNA), developed by Dumas et al., Nucleic Acids Res., 19:5227-32 (1991). The major differences in procedure are that the RNA is alkaline hydrolyzed after reverse transcription and RNA ligase is used to join a restriction site-containing anchor primer to the first-strand cDNA. This obviates the necessity for the dA-tailing reaction which results in a polyT stretch that is difficult to sequence past.

An alternative to generating 5' or 3' cDNA from RNA is to use cDNA library double-stranded DNA. An asymmetric PCR-amplified antisense cDNA strand is synthesized with an antisense cDNA-specific primer and a plasmid-anchored primer. These primers are removed and a symmetric PCR reaction is performed with a nested cDNA-specific antisense primer and the plasmid-anchored primer.

RNA Ligase Protocol For Generating The 5' or 3' End Sequences To Obtain Full Length Genes

Once a gene of interest is identified, several methods are available for the identification of the 5' or 3' portions of the gene which may not be present in the original cDNA plasmid. These methods include, but are not limited to, filter probing, clone enrichment using specific probes and protocols similar and identical to 5' and 3' RACE. While the full length gene may be present in the library and can be identified by probing, a useful method for generating the 5' or 3' end is to use the existing sequence information from the original cDNA to generate the missing information. A method similar to 5' RACE is available for generating the missing 5' end of a desired full-length gene. (This method was published by Fromont-Racine et al., Nucleic Acids Res., 21(7):1683-1684 (1993)). Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcript and a primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest, is used to PCR amplify the 5' portion of the desired full length gene which may then be sequenced and used to generate the full length gene. This method starts with total RNA isolated from the desired source, poly A RNA may be used but is not a prerequisite for this procedure. The RNA preparation may then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase if used is then inactivated and the RNA is treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase. This modified RNA preparation can then be used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction can then be used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the relevant gene.

The present invention also relates to vectors or plasmids which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC (e.g., as described in columns 2 and 3 of Table 1A, and/or as set forth in Table 1B, Table 6, or Table 7) is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as described, for example, in Table 1A and Table 7. These deposits are referred to as "the deposits" herein. The tissues from which some of the clones were derived are listed in Table 7, and the vector in which the corresponding cDNA is contained is also indicated in Table 7. The deposited material includes cDNA clones corresponding to SEQ ID NO:X described, for example, in Table 1A and/or Table 1B (ATCC Deposit No:Z). A clone which is isolatable from the ATCC Deposits by use of a sequence listed as SEQ ID NO:X, may include the entire

coding region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Furthermore, although the sequence listing may in some instances list only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to sequence the DNA included in a clone contained in the ATCC Deposits by use of a sequence (or portion thereof) described in, for example Tables 1A and/or Table 1B or Table 2, by procedures hereinafter further described, and others apparent to those skilled in the art.

Also provided in Table 1A and Table 7 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res. 16*:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res. 17*:9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies 5*:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus 15*:59- (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res. 16*:9677-9686 (1988) and Mead, D. *et al., Bio/Technology 9:* (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the deposited clone (ATCC Deposit No:Z). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes

corresponding to SEQ ID NO:X or the complement thereof, polypeptides encoded by genes corresponding to SEQ ID NO:X or the complement thereof, and/or the cDNA contained in ATCC Deposit No:Z, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA sequence contained in ATCC Deposit No:Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X or a complement thereof, a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or the polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or a polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, a nucleic acid sequence encoding a polypeptide encoded by the

complement of the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA contained in ATCC Deposit No:Z.

Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in Table 1C column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in Table 1C column 6, or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1), or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1) and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described

polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2), or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2) and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (See Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of Table 1C column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary

strand(s) of the sequences delineated in the same row of Table 1C column 6, or any combination thereof. In preferred embodiments, the polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in the same row of Table 1C column 6, wherein sequentially delineated sequences in the table (i.e. corresponding to those exons located closest to each other) are directly contiguous in a 5' to 3' orientation. In further embodiments, above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1C, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1C, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1C, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1C, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A, Table 1B, or Table 1C) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO:X correspond to the same Clone ID. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A, Table 1B, or Table 1C) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of

SEQ ID NO:X correspond to the same row of column 6 of Table 1C. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X are directly contiguous Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1C are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1C are directly contiguous. Nucleic acids which

hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides, are also encompassed by the invention.

In further specific embodiments, .polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of another sequence in column 6 corresponding to the same Clone ID (see Table 1C, column 1) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one sequence in column 6 corresponding to the same contig sequence identifer SEQ ID NO:X (see Table 1C, column 2) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of another sequence in column 6 corresponding to the same row are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1C, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

Table 3

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. Accordingly, for each contig sequence (SEQ ID NO:X) listed in the fifth column of Table 1A and/or the fourth column of Table 1B, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, b is an integer of 15 to the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. More specifically, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a and b are integers as defined in columns 4 and 5, respectively, of Table 3. In specific embodiments, the polynucleotides of the invention do not consist of at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. as disclosed in column 6 of Table 3 (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone). In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby incorporated by reference in their entirety.

Table 3

cDNA Clone ID	SEQ ID NO: X	Contig ID:	EST Disclaimer Range of a	Range of b	Accession Number's
H2CBU83	11	884134	1 - 2689	15 - 2703	BE613316, BE739453, AW961199, AV658769, BE785673, AW963999, BF037119, BG030580, BF036149, BF699154, BF033837, BF697524, BF695458, BF036638, BF701778, BG030507, AW377122, BF665913, BF699078, AW377125, BF665294, AV658829, BF667082, BG166746, AW851261, BF241480, AW850925, AI978869, BF695890, AA845339, BF668201, BF699860, BF085620, AA405940, BE612726, BF666583, BF667787, BE739116, BF665805, AW752845, BF701466, AI800939, BG121547, AI620357, BF700054, AW851052, AI924880, AW752835, AI800807, BF697582, BF700919, BF667321, AI139396, BE958619, AV692286, AI955392, AW752844, BE042841, BF698625, BF244588, AW440250, BF698345, AW152584, AW955901, AI671911, AA535832, AW850982, AI935579, BE089877, AW752868, AI683119, BF130660, D61864, AW630835, AI621153, BF514638, BF697211, AW192136, AI286255, AA403153, D62117, AW028833, N78154, BF154792, BF665821, AI538061, N64201, AW851056, AW938593, BE093579, AW938596, AA928873, AV651183, BE817020, AV657915, AV657131, BF666276, AV660141, AI699025, AI016115, R66206, N45586, D61708, BE868472, AA403241, AV657914, AA313513, AV682813, H88565, AA531589, R58698, AA857811, H42631, AA307010, R67084, BF334107, AW971385, R68027, AW021104, AW296538, BG166828, AI887214, AW468968, R64487, H88521, BF697149, R94825, R68028, R92884, R65584, AA377208, AI050980, AA318641, D62093, BF813323, N78160, T73957, D61982, D62303, D62026, AI806100, AA095925, N56560, T73925, AA507092, BF750358, BE148612, BF750357, BE867141, T73948, N88292, T73916, BE044052, H95089, H73281, AV660091, AF257182.1, AF346711. 1.
H6EDC19	12	543259	1 - 746	15 - 760	AI090153, AI767722, BG116691, AI797075, BF528376, AI698172, AI681570, BE671343, AI539236, AV704244, AI539246, BE264613, AA864681, AW204700, AI808925, BE676036, T79284, BF445461, AA400027, AI209219, AA300244, AA427390, AA302217, AA252421, AA406631, AI869251, BF969629, AI262951, AI498669, AA300243, AW072158, T79197, AA411721, AV682333, F34003, AI123608.
HACBD91	13	637482	1 - 1431	15 - 1445	AI123694, AA203656, AV707802, BF575227, N77966, AW956121, N71852, BF732312, AI338999, AA704675, AI742966, AA176725, AV744696, AI039168, AA329423, AA680411, F10345, T85994, AV682639, AA731436, AV735262, AV733694, AA505796, AW959998, BF793146, H79631, R00088, BF978632, BG034327, AV716953, AW955313, BG032189, AV717860, AV716893, BF244606, AV733654, BG030662, AI802907, AA528524, AA973692, AA658895, AV714250, AV718258, AV716004, BF029739, F26324, AW772717, BE909294, AA370595, AI392630, BF529817, AI914394, BE748127, AA975366, BF029799, AI126532, AA977864, R38577, AI093884, AW264528, AI351443, AA916014, AA359165, AA594324, AI682171, AA404535, BG034254, T75123, AI832970, AA973611, AI833308, AI814033, BE781781, BF035996, BF036344, AA888167, BE541776, BF109665, BE551387, AI268514, AV710503, AI709250, F33691, BF216659, F33502, BE467615, AV738506, BE503802,

					AV763934, BG110890, AV742881, AV710956, BF965198, BG033031, T90966, R02459, F32392, BF029956, BF690853, AV764373, BE738142, BF244383, AW772766, BF978393, BF030821, BE548289, N64163, BF576733, AW872492, BE218579, BE539011, BE042987, BF978138, BE217894, BF692527, AW419258, BF219313, BF244019, R02355, BF242775, AA340839, AW440167, F30529, BE748667, AA640120, BG179795, BF679132, BF382290, AI719390, R35603, BF240791, BF691038, AW009337, AA886535, BE738709, AI253328, AW268515, BF977850, H79632, AV764541, BF214426, BE184678, BE171856, BF382191, F12739, BF031722, BE564110, F21702, BF219100, F26311, F27624, F31646, F24066, F30253, F21442, BF030470, BF215493, AA365400, AV725369, BF243623, BF216495, F23622, R38445, Z20180, F23439, BF031636, AA340808, BF246303, F29361, BF212059, D19917, BF210763, AI720401, N58379, AA706899, BE737668, F37786, AC009289.8, BC000855.1, AF044957.1, AC008804.6.
HAGAQ26	14	561996	1 - 1319	15 - 1333	BF111995, BF111899, AW051348, AI807015, AA349378, AA349433, H05458, T39468, T39511, F02812, T50009, T50073, Z43427, AI372659, BE843943, BE843903, AA860404, BG015163, BE938621, BE843892, AI372657, BE698483, BF092079, BE301746, BG015653, AA496848, AL045349, BE047833, BE965724, BE965432, BE875407, BE964497, AW059713, AL037454, BE964512, AL119836, BE967307, AI918408, BG180506, BE964876, BF924856, AI683559, AW151136, BG107576, BE965067, AW268261, AI691088, AI798271, AV689111, BG253692, BE011885, AI868163, AI918634, AW084097, BE875022, BE879931, AI340603, AV728806, AL036652, BF814335, AI370392, BE963838, AV725920, AW021717, AW089036, BE877142, BE964795, AI469516, AI805638, AI925404, AA291456, AL040694, AI285439, AA888196, BE966404, BE965758, BE965355, BE544111, BG180273, AI366968, AW022682, AV742698, AI560679, AI345608, BE967149, AI366959, AI473536, BG153056, BE964614, BE540578, AI349933, AI623736, AW020095, BF038804, BE908276, AV742475, AI345471, BE966787, AI343091, AI345677, BE966011, BE965621, AI340519, AW162189, BF814357, AW198144, AI446809, AV717295, AV716613, AV682144, AI366992, AA806719, AV682099, BE964661, AA789133, BE963918, BE904051, AW023338, AV738730, BE873776, BG027082, BF032404, BG164035, BE613727, BG032219, AI863357, BF965884, AL048323, BG153050, AI636719, AV756658, AW827289, AL048340, BE879905, BG109270, AW020693, AI686576, AW858254, BE964073, AI470293, AW827290, AW058233, AL038605, BG107625, AI702527, BG260037, AW834325, BE047952, BF793031, AA643235, AI418254, AI623905, AI538764, AI524654, AI249946, BE964006, AA848053, AV733819, AA635382, H42825, AI929108, BF924884, BG029053, BE974031, AI473451, AV711509, BG252714, AL048644, BF868927, AL040241, BE883591, BF968622, AW068845, AI624293, BF813196, AW022494, BF340323, AL046463, AW020288, AI521596, AW021373, AW162194, BF915316, BF925370, BF886214, AI923989, BE965481, AI868204, AI242736, BE891942, BE735380, BF909758, AA579232, BG166687, AV715354, BE964767, AV756247, AV758825, BF814449, AL038445, BE965121, AW163834, BF343521, AW084056, BG032169, BE904851, BF868811, BG104782, AI537677, BG122101, AI628325, AI590645, BE875402, AW083804, AI561299, BE908335, AW059828, BF753056, AI559863, AV726125, BF750879, AW265004, F26535, AI583032, BF811808, AI366974, AI355765, BF822127, AI609593, AI887775, AI858865,

					AI500061, BG121959, AA572758, BF699668, AI348897, BE778024, BF814504, AI345224, AI357599, AV681949, T99953, AI589428, BG113851, BG110517, AL530922, AF169301.1, AC091736.1, AL442082.1, AB049853.1, AL389935.1, BC007364.1, S78214.1, X99717.1, AL122121.1, AK027161.1, BC006195.1, BC001418.2, BC005858.1, AK000310.1, S77771.1, AL389939.1, AF090900.1, AF090934.1, BC003104.1, AK025092.1, AK024524.1, AB047897.1, BC007674.1, AB044547.1, AL136789.1, BC004874.1, AL122045.1, AK026506.1, AL389978.1, AL049464.1, AF067420.1, BC007355.1, M86826.1, AB063071.1, AL110196.1, BC001293.1, BC007998.1, BC006287.1, AL096751.1, AL133565.1, AF057300.1, AF057299.1, Y10080.1, BC008387.1, AK026518.1, AL133081.1, AL162006.1, U42031.1, AK027142.1, U51587.1, AF177336.1, AK000137.1, AL157479.1, AL137547.1, AL133093.1, AB063008.1, AK025431.1, AL390167.1, BC008673.1, BC000317.1, AB047869.1, AF205861.1, BC003650.1, AL133560.1, AK024538.1, BC000799.1, AK026480.1, AF218014.1, AL049382.1, AK027182.1, AK000421.1, AK000323.1, S76508.1, BC001774.1, AB051158.1, AB047615.1, AL137523.1, AL353957.1, U58996.2, AB055303.1, Z37987.1, AB060887.1, AK026452.1, BC008025.1, AL050170.1, BC003687.1, AK026395.1, AB060912.1, AL122111.1, AB060863.1, BC005160.1, AB056809.1, AB052191.1, Y14314.1, AK026927.1, AL096744.1, AL137658.1, AL137705.1, AL137292.1, BC000778.1, BC008185.1, S61953.1, AL137283.1, AF097996.1, AL049430.1, AL390154.1, BC006164.1, AL512718.1, AL049314.1, J05032.1, AL117583.1, AB063046.1, AF110640.1, BC001349.1, AF120268.1, AK000212.1, AK000083.1, BC006180.1, AK027164.1, AB047801.1, BC007534.1, BC000556.1, BC004905.1, AL110224.1, BC007021.1, AK026462.1, AL356278.8, AF162270.1, AL050277.1, BC008070.1, AL512684.1, AB047966.1, BC006408.1, AF225424.1, AK000655.1, AB060856.1, AK025573.1, BC001056.1, AB047631.1, BC005890.1, AL137273.1, BC004370.1, AF207829.1, BC002491.1, D83989.1, BC004943.1, AF239683.1, BC005007.1, AF111112.1, AL122049.1, BC009033.1, L19437.2, AK026086.1, AB060883.1, AK026045.1, AB056420.1, AF305835.1, AB060903.1, AK026434.1, AL133568.1, AL122118.1, AL050393.1, AL137476.1, AC023880.5, AL117435.1, AK026534.1, BC000348.1, BC005678.1, AJ001838.1, S78453.1, AL136767.1, X76228.1, M64349.1, BC005151.1, AB055370.1, AB060893.1, BC001963.1, AF159615.1, AK026603.1, AL512689.1, AL133075.1, BC007680.1, AL136754.1, AK025708.1, AL050146.1, AF217991.1, AL117440.1, BC007897.1, AL136766.1, AL117629.1, BC006133.1, AK000450.1, AK026592.1, AF003737.1, AL050024.1, X69819.1, AB049900.1, AK025958.1, AK025084.1, L30117.1, AL080074.1, AB048974.1, AB063084.1, BC002471.1, BC006411.1, AK025772.1, AF090896.1, AL137488.1, BC000066.1, AK026551.1, U77594.1, BC002777.1, AL353802.14, AF271350.1, BC000632.1, AK026533.1, BC009026.1, BC003683.1, AK027096.1, AK025414.1, AB050411.1, AK027104.1, AK026353.1, BC002541.1, BC004297.1, U39656.1, AK026522.1, AB050534.1, AL136644.1, BC006440.1, AK026885.1, AK026571.1, BC003682.1, AK025541.1, AL136843.1, BC004431.1, AF132730.1, AF219137.1, AL137574.1, AF090886.1, AL136893.1, AK024944.1, AK025015.1, AL050116. 1.
HAGDS35	15	1352199	1 - 737	15 - 751	AI803504, AI261590, AW970422, AA430349, AI017015, AI217649, AI357214, AA425610, AW170513, N21542, AI805514, AA535732, AI922416, AI089295, AI807997, BE549761, BF434916, AI093989,

					AI537981, BE464016, AI128724, AA046439, AW970309, AA211360, AA974447, BE672109, BE466566, AI990335, AI655816, AI479968, AI926934, AI961572, AW970221, AW243397, AA534329, AW593487, AI283132, BF115098, AA256606, AA019380, BF061520, AA936249, AI446563, AA872374, AA011475, H25408, AI393572, AI203429, AI961183, BF735047, AW613954, AI216786, AI798452, H28374, C01415, AW016511, BE551700, AA730296, AI991488, BF476167, AA455164, AA516090, R46342, R43067, R35671, H39555, AA258077, AI950123, Z38679, AL535820, AW887425, AW958078, BE771685, AI382468, AA971129, AA090871, BF971621, AA455366.
HAJAN23	16	135236 4	1 - 2835	15 - 2849	BF337092, BF968693, AI949422, AL523556, BF798043, AV702522, AI423046, BE883392, BE786755, BG178390, BE408282, N31952, AA465612, AW195192, BE543143, AI564487, AV660395, BE543045, R88931, BE825704, AA658285, AW975104, AI740792, BE002027, BE928231, R89611, BG168885, BF331860, AW590726, AA641596, AA313322, BF358320, AW418507, AW842226, AI949987, AW615497, AW194161, BF222524, BF197303, BF755611, AI869038, AW243485, BF754745, AI367183, BE073382, AW013907, AF310971.1, AF301000.1, AB050049.1, AF261884.1, AC010279.4, AB050050.1, AK025591.1, AL079298.1, Z70695. 1.
HAJBR69	17	638516	1 - 741	15 - 755	BE262907, AW503376, AW503644, BF982382, BE079288, AW504239, AA701415, BF315343, BE277664, BF921555, BF736464, BF756620, BE720223, BE815902, AA490675, BE930704, AW971745, AW804686, AW392670, BE695785, AW861944, AW604723, AW877209, AL119483, U46351, AW858526, AW858525, AL042984, AL119497, AL119324, AL119319, AL119355, AW500561, U46349, AL134538, AL119457, BE705903, BE705906, AW577135, AW372827, AW384394, AW861889, AW858455, AW363220, U46350, Z99396, AL119484, AL119363, AL119391, U46347, U46341, AL119443, BF868687, AL119444, AL119341, BF868697, AW604726, AL119439, BF868684, BE705905, AL119522, AL119396, U46346, AL119335, AL134531, AL134533, AL037205, AL134920, AL134525, BE705904, AL119399, AL043029, AL119496, AL119418, AW861954, U46345, AL043011, AL042614, AL042975, AL043033, AL042544, AL042965, AL134542, AL042450, AL042542, AL043019, AL043003, AL119464, AL042551, AB028986.1, AB026436. 1.
HAMFE15	18	905695	1 - 4115	15 - 4129	AL530791, AL530792, AL529741, AL535065, AL535066, AU124538, AU133125, BG248951, BG170992, BF342607, BE791618, BE788808, BE889885, BE899228, BE266316, BF666992, AA604226, BE855814, AA858439, BF306389, AW965351, AI459262, AI949460, BE566846, AI920795, BF695661, AI628581, AI810626, AA213464, BF436958, AI765166, BF131526, AA446901, BE669483, BF105045, AA165298, AW300022, N48825, AA595754, BE218460, BF126313, AA165297, BE044264, AI686706, AW300346, BF760498, AI472286, AI804402, AA426331, AI278834, AW169453, AW239143, AA426332, H29503, AW602873, AA213575, BF376918, AV749783, AA075971, AA447021, AA074072, BE244841, AI002939, BE832901, AA598694, BE694349, AI471852, AI961851, AW136228, AI422999, AA707156, H29787, AV692260, AV692283, AV692263, BE243932, BE244952, BF330518, AV698872, AA333388, AV698900, AV691373, AV695584, AV694677, AV687965, AV696854, R13303, AA564851, AI762353, BF751566, BE244135, AV690233, AV696838, BE463584, T05291, BF878149, BE258595, N55929, AV698875, BF238880, AA348529, AV689303, T78749, BF736483, BE674953, N89249, N45617,

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HAMGR28	19	892971	1 - 1660	15 - 1674	AL519641, AL519640, AL525613, AL526308, AL527643, AL530324, AL525663, AL525671, AL530325, AL515833, AL515832, BF313053, AL527577, BF529163, BE312001, BF984557, BF530620, BE396752, BE304484, BF983145, BE560368, BF316599, BG114646, BE269376, BF313413, BE298748, BE440179, AW953553, BF307907, AW978612, BE617303, AA845426, AI830874, AI983227, AW956917, AW410199, AW628335, BE464326, AA530876, AW452186, BE139083, AI829507, AI356849, W69111, AW084551, AA406233, AI589504, AI970964, AI420766, AI701901, AI130010, AI288363, BF571959, AI683363, BE019516, BE206283, AW272707, N23238, AA593625, AI000296, AA406505, AW593667, AI933020, AI337797, BF691989, AI139514, BF062876, W35301, AI418519, AV759081, AW514035, AW004995, AW591716, F28754, AA815275, AI347528, AI624104, AA574436, AI817434, AI025110, T08849, AL527576, AI079740, AA962799, AA707405, BF445536, F37186, AW207522, AW591663, AW263070, AW510310, AW264517, AA028008, T33149, AA723895, W69236, R40168, T23442, H88132, H78378, AW514039, D12424, W23701, F34521, Z43089, BE646197, AI475064, AA653748, AA312858, AW959275, AW410198, AI932423, AA121114, AA121036, AA295884, AA356831, AI310743, BF513002, AA381766, Z39180, R12971, AW379122, AI768799, BE877018, AI560685, AA338084, AI810799, AW861944, AW750703, F24446, AW972092, AW858525, AW877209, AW968355, AW968356, AW972093, AW968729, AW971740, AW972091, AI431351, AW972090, AW969229, AW858455, AW804686, AL119324, AI432644, AI623302, AW604723, AW858526, AI432647, AI432653, AW081103, AI432661, AI492519, BE672748, BC007438.1, AC004150.8, AF064854.1, AB026436. 1.
HAPOM49	20	769555	1 - 1991	15 - 2005	AL520731, AL520732, BE271092, BE271295, BF111901, AV650049, BF686278, BE840511, BF111645, AI809801, AW168904, AI809806, AW103024, AA933973, AI744944, AI588991, AI033486, AI096548, AA662523, AW468813, AI950317, AI279302, AI096696, BF239172, AW662564, AA417671, AI189300, AI753808, AA235373, AW960081, AI095057, W86920, AW189373, AI361321, BF061913, AI366754, AI218487, AI824959, AI348339, AI032926, AV659024, AA889791, BE243641, AA626261, AI338100, AA417558, W24077, AW974720, N72014, AA894657, N59290, R01247, AA235784, BE929365, BE929364, BE244396, AI275184, AI810247, W24089, R36924, AA356938, N91904, AA508411, AA649828, N91912, N99466, Z24931, H68902, BE782571, BF840140, AC004067.1, AF332892.1, AF306567. 1.
HATBR65	21	635514	1 - 798	15 - 812	AW754098, AV747079, AW964560, BF827304, AI697254, AA826321, AA663880, BF924786, AA772037, AV725414, AA826164, AA663006, AA826322, BE062047, AA835931, AA319870, R95053, AV760830, BF918713, BF959165, AI053538, BF930635, BE828744, AA078591, AF139781, AA491430, AA078183, AW393403, W74390, AW578861, AW393400, AA320812, BF840307, AA078213, AW752269, BF757569, AA077448, BG004304, AW793003, AA047825, AA001509, AA076683, AW857010, BE183669, BE183617, BE699552, AV720211, AW973541, BE932909, AI254770, AI284543,

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HAUAI83	22	639009	1 - 896	15 - 910	BE439675, BF984328, BF978147, AW955502, BF337207, BE272543, AV757236, BE903592, BF212880, AW405217, BE743902, AI991315, AV701663, BE270100, BF681301, BG178791, BE222645, BG167626, BF132414, AW069149, BF238307, AV736544, BG255905, BF698492, BF130460, BF102497, AV745093, BE543668, AI493727, BE254068, AA934591, N24442, AI147316, BF680700, AV705947, BE734398, BG231583, BE256074, AV754408, AW014782, AI198642, BE646408, AA889969, AI709288, AW135010, AA877730, AI720901, AA496681, AA995328, AI032868, AW579254, AI186312, AI969715, AI660672, N23673, AA420567, AA427691, AI188938, AA471213, BG117664, BF102532, AI191317, AI332586, AI219152, AW000829, AI470155, AA843102, AI125390, BE312355, AW182893, AI141484, H93124, AW000718, AI268069, AA815421, AA708211, AA129884, AI023128, AI147588, AV724436, AA159902, AI129253, AA290635, AV706639, AI127280, N58266, AA315771, AI673417, AI587141, AI186000, AI142324, AI128437, AA723220, AI335350, BF687940, AA552070, AI087415, AA995933, AW300769, AA862543, AW008043, R68241, BE349483, AI241459, AI355685, AW304225, AW083014, AI277068, AI038096, AI160884, AA774420, BE407927, AA810159, W37128, W04866, AI828898, AI093015, AA732834, AV707544, AI934627, AA026633, W01678, H84951, AI279658, BF665006, AA419151, AA844949, AI096712, N71609, AV735174, N69652, AA159798, AI969153, AV729015, AA149944, N95063, AI798245, AV736793, AA771923, H20023, R99610, H50207, AA653091, N70496, AW104010, H40779, N33986, D55334, AV743438, AW130386, BF977248, AI125700, BE091971, AA572869, W00449, AI744165, AA157561, AA531221, AI275921, AA969778, H95780, N92248, AI159958, N38815, H20143, AI680770, AA305332, N77862, AV738026, N72206, AA037790, AI752109, AV743648, AA937128, AA962124, AA478395, AV741494, AV740102, H19070, R71518, H18782, R94908, BE621803, R77435, H99652, AA694460, AA641831, H21165, AW511932, AI184349, W38900, AA844297, H46188, W58208, W40195, R71470, N94261, T31343, BE620993, R70469, BE909620, N25251, AI752110, AV741554, AA165011, AA037789, H01343, AA643896, R77524, H23656, R70556, T30654, W37143, AA326924, C01763, R91937, W32075, H60231, R92265, H69010, H67121, H71491, H18688, R09629, H38970, H27857, AA558120, R94992, R09517, H75393, R99715, H23612, AA326929, AA026672, BF436567, H01135, N54428, AA186949, T32463, H59520, AA339137, H39170, AI709334, R86746, N33887, R68534, AA305400, N58289, AI351248, AA410643, AC010422.7, AF151898.1, AF059620.1, BC001192.1, T52716, T61025, T61577, R26656, R79694, H03303, H03402, H18972, H22368, R87112, H60187, H60393, H81427, H84495, N71651, W31583, AA164972, AA188345, AA419096.
HBAMB15	23	671835	1 - 807	15 - 821	W27833, AI860764, AA809619, BF432929, AA768248, AI370876, AV748724, AI291737, H96013, AW051697, AI633038, AI784315, BE546233, BF980899, BF977483, AL138479.4, AL132855.4, AL121755. 23.
HBGBA69	24	135228 9	1 - 967	15 - 981	AL520900, AL520550, AL520551, AL521649, BG029889, AV704088, AW372721, BE264987, BE906201, AL037829, BE782595, AA779652, BF724791, AW372704, AL037830, BG104612, AA722880, N21569, AA478642, AA447813, BE349318, BG254734, AI168324, BE047392, AW131642, AI590628, AA410845, AL520901, AI829611, AA447814, AI359892, AI142945, AA252189, AA974206,

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HBIAE26	25	514418	1 - 1024	15 - 1038	AW237905, AI635440, AL079734, AV729929, H73550, AI669421, BE092488, AC004076.1, AY030284.1, AL139353.3, AC008569.6, AC011479.6, AL031659.9, AC083865.2, AL353807.18, AE006464.1, AL136979.16, AL163032.3, AC019097.5, AC015651.18, Z93023.1, AC011484.4, AC013449.8, AC005015.2, AC006120.1, AC084865.2, AC022116.5, AL512449.6, AL109797.18, AC005736.1, AC006008.2, AL022336.1, AC006329.5, AC002302.1, AL357515.26, AL035669.43, AF288742.1, AC005522.2, AC005840.2, AC021016.4, AC078962.30, AP002851.2, AL138787.11, AP001695.1, AL160269.14, AC005512.1, AL034420.16, AL354932.26, AC005088.2, AC011500.7, AC008666.5, AC010404.5, AC000353.27, AC011469.6, AL139384.16, U91321.1, AC005355.1, AL024498.12, AC008755.6, AC020552.4, AC008641.6, AL356970.21, Z97876.1, AC005046.3, AL022326.1, AC007388.3, AL451075.15, AL390374.16, AC026431.3, AC011497.6, AC009120.8, AC010267.6, AL158207.15, AL590762.1, AL137229.4, AL135978.4, AL133454.6, AC008901.5, AC008752.6, AC002045.1, AC006211.1, AP002982.2, AC002301.1, AC004106.1, AC004089.25, AP001752.1, AL138733.15, AC006449.19, AL121992.24, AC015550.18, AL035420.15, AC067941.7, AC004900.2, AC008786.6, AL109743.4, AL121578.1, AC018639.8, AP002812.3, AL033383.26, AC010913.9, AC024561.4, AC010618.7, AC020916.7, AL157877.11, AC018758.2, AL035071.17, AC002470.17, AC004922.2, AL035422.12, AC006597.2, AC011236.8, AC006480.3, AC007597.3, AL357315.14, AC000360.35, AL353135.32, AC022217.5, AC005531.1, AC008946.6, AC008264.10, AL049539.21, AC008655.6, AL138784.30, AC006538.1, AF129075.2, AL356257.14, AL034417.14, AC008440.8, AC005920.1, AC009131.6, AL121826.11, AC005480.3, AC083871.2, AL139385.12, AC007683.5, AC011452.6, AC008155.9, AP000555.1, AC009470.4, AC005077.5, AF064861.1, AL139809.16, AB003151.1, AL136105.9, AL049776.3, AC008745.6, AL031774. 1.
HBINS58	26	135238 6	1 - 829	15 - 843	AI827239, AW104045, AL536345, AL096774. 9.
HBNAW17	27	526797	1 - 587	15 - 601	AA713518, AA807610, AW104604, AA830415, AW975518, AL138824. 19.

HCE2F54	28	634016	1 - 1262	15 - 1276	AL530657, AL534642, AL519887, AL519439, BE257752, AA769913, AI609266, BE674973, AI652143, BG057242, BE046399, AI669608, AU157638, BF347064, BE046435, AI571552, AA406626, AI634414, AW731848, BE245626, AI372990, AW473891, AU153165, AA969877, AI458122, AA402109, AU157487, AI815017, AA936365, AA481847, AI052565, AA704608, AI860561, BE736308, AI591232, AA425187, BF685966, AA479747, AI922541, AA889587, AA992245, R47377, AV694506, AA707462, AA283778, BF589042, AI767815, AW439290, AI354234, AW630387, R82068, BF829195, BG152634, AA229272, BE246763, AI745410, AW074728, AI867440, AA405028, AI652744, AI799388, AW732540, AA724063, AI249812, R43967, BE247615, AA229721, AA290883, AA477093, BF847615, AW117313, AA425298, AW804421, AV661367, AW627358, AA456146, W45494, R82878, R82020, F35061, H01485, AW014040, F25139, AA339640, AI961334, AA478233, AA362857, AA326205, BE244646, AA229827, AA377429, AI186501, BG008599, BE242784, T32225, AV686564, AA688260, AI085847, AV686569, BE157547, AA860204, R08559, F09429, AA405272, BF845336, BF380796, BF380795, AI860044, AA883556, AA032260, AA332516, AA402982, AA332325, BE157532, AA336006, Z39018, AI695855, AI589935, AI583010, AI954634, BF841145, AW469249, F04759, AA032193, F04962, AI524382, BF922668, BE157535, H01586, AI298047, T89862, AL530658, BF883965, BF374266, M78413, BF883968, AW197535, AW952615, BF847600, AW007397, BE157466, AI907687, AI632570, AL519888, AK023173.1, BC007642.1, BC007864. 1.
HCE3G69	29	728432	1 - 2070	15 - 2084	BE740754, BF339727, BE740538, BE277589, BE382940, BE618822, BE793142, BE390135, BF530091, AW969581, BF315345, BF340007, BG164152, BE618316, BE277504, BE740158, BE542020, BF527796, BF796337, BF310510, BE409091, BE545069, BE312476, AI979049, BF314374, AI828148, BF528364, BF341988, AA987262, AA789210, BE783336, AA552222, BE042994, BE408361, AA542834, BE262213, BF724352, BG170449, AA399248, AI399975, AA682879, AA709002, AA628073, AA523036, AI281261, AI749652, AI148325, BE297932, AI347619, AI206709, AI857651, AI304965, R77325, AI523697, AA349818, T16002, H56978, N95160, AA351179, BF736456, BF919187, W16789, R61061, AA994296, BE872104, AW131936, T77786, BF805555, R42239, AI001897, R49103, H27917, AI216183, BF435415, AA349337, AA293132, AA349338, H47705, BF690107, BE909738, BE831416, T87999, R77274, AA017080, AA293765, H47615, W21536, R64334, H56891, BF813356, BF957635, BE827070, AI560786, R64335, T77787, AW380761, AI027520, AW380835, AI870267, AI263580, BE563729, AA324593, AA588228, AW955408, AI277032, R18259, AI566653, T33783, AW883586, D53543, BG105324, AW452975, R60940, H41337, R36021, T32921, BF895461, AI360103, AW380828, BE256741, AA057061, AI564056, AW327298, AI244916, W35216, BE262875, AL040896, BE501695, BE351024, BF058407, BE263311, T15786, AA812926, AA830661, BE693588, AI797886, BF314562, AA299346, AW451523, BF337822, AI520932, D80870, AA333807, AA058540, AW363994, AW604788, AW820702, AW820474, BF848412, BF312802, BE171868, AW604793, AW273608, AA610114, AA865732, AW363958, AA524542, AI089686, AA359625, W23626, D20577, AI150519, W31778, AI150517, AW997867, AV704757, AV706824, AV705873, BC002420.1, AL136758. 1.
HCE5F43	30	612796	1 - 1751	15 - 1765	AL525531, BG034956, BE858832, BE897817, BF510434, BG253874, AI656560, AI628821, BF215392,

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HCEFB80	31	114340 7	1 - 2480	15 - 2494	BF343021, BF339312, BF341481, BF967606, BF344530, BF344213, BF513319, AI393526, BE857064, AW016800, AI937454, AI370995, AW170034, AA416907, AW044650, N75664, BF341415, AW960857, BG222497, AA703765, BE855450, AU146334, AA703342, N64813, T23840, AA446784, AA228781, M86149, T08275, AA386225, AA417008, AI671567, T15689, AW128975, AA432098, H83023, M85314, AI277779, BG222958, BF923571, M79106, BG152559, R13095, R11764, R21361, BF921573, F05369, T28040, T10247, AA323697, AI361427, AW235399, AI352392, T10246, R37689, AW594074, R40527, H82804, N59328, BF894586, R46460, T15861, BE672078, C14288, D25217.2, AF319633.1, AL022327. 17.
HCEWE20	32	543370	1 - 871	15 - 885	T51653, AW168798, BG059728, AW151307, AA189081, AL133942, AI924175, AI610776, AI034217, AI479035, BE165748, AI811494, AW090210, AA346162, AW167452, AI687804, AI749571, AA470572, AW089655, AI197934, AI827133, AU144339, N64574, AA470493, AI697247, AI937684, N76274, AI984510, AL047920, AA223830, AA493998, BE176566, AV730063, T62931, BE148908, AA876415, AI801377, AW589501, AA085707, AW177317, AI439860, AI813517, AA581340, AI858607, AA099491, AA613244, AI887321, AA643785, AA633390, AU143906, AV719347, AI362951, W58428, AU146966, AA847621, AI564253, AI921101, AL041417, AA643823, AI567544, AI733077, AW177120, AI561208, AI264673, BE158597, AU145674, AA130536, AA694579, N74502, N54295, AW440317, AF063514, AU119100, AA873103, AW177237, AA160519, AA197059, AW177231, AW177264, AA598786, W49501, AA911409, N26540, BE264670, AL036881, AU146974, AA493751, AW994225, C17730, AA724159, AU145383, AA157033, AA041332, AA166854, H96719, AA055654, H65500, AA219480, AU148220, AI935333, AL523955, AI132962, AW084901, N48690, AI862874, D29455, AA598990, BE044603, AF074627, AV730577, BG235936, AA878800, R94112, AW275729, AI376984, AI951835, AA101456, AA503213, AW440351, AI735074, AW177266, BE904846, AA846188, AW177226, BE152426, AA493735, AA593081, AW615437, AI538654, AA404968, AW813744, AA669580, F03370, AA350922, AA356989, AI421079, AV728282, AW771706, N76124, AI189033, AA584498, AI961771, AA953572, AV719696, AA467957, H04879, BE159220, T69889, AV720543, H97020, AA467904,

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HCGMD59	33	636078	1 - 776	15 - 790	AI346379, AW009453, AA477432, AA152289, BE219294, T27069, AI745607, AW852105, AI807602,

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HCNDR47	34	1016919	1 - 1329	15 - 1343	AI621217, BF222897, AA632651, AI950250, AW139452, AW207039, AA505117, U69203, AI949187, AW953975, AI160725, BE348367, AI631345, AA707909, AA535510, BG059719, AI680791, AI700776, H17406, AA524577, AA062981, AA365529, H16756, AI699070, AW970783, BE858688, AI696027, BF766585, AV709230, BE220337, AW194354, AA365530, AA678861, BE707377, AL122003.17, AB007895. 1.
HCNSM70	35	637547	1 - 1075	15 - 1089	AW170355, BF437750, AA781956, AA304933, BG260457, H48606, AW517161, AA088807, BE004003,

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HCUIM65	36	550208	1 - 861	15 - 875	BE781101, BE540200, AI972511, BE300952, AA464837, BG150212, AI681901, AW172458, AA099207, AW205564, AW408650, AW205714, AA450308, AA636047, AI656442, BF437116, BE466112, AW575656, AW962721, AW206882, AA099221, AI620473, AA369585, AW469939, AW136836, BE547752, AI638262, BF059133, AA236642, BE551958, AW086133, AI917742, AI623315, AC005391.1, AL445584. 16.
HCWDS72	37	707833	1 - 306	15 - 320	
HCWKC15	38	553621	1 - 696	15 - 710	AW504485, AI380617, AW805539, AV758903, AL079734, AA916430, AW819125, AV762982, AI625604, AI792575, AW084445, AW975210, BE138594, AW069227, AW023111, AV764259, AI792521, BE501593, AW021583, AI890324, BF725844, AW438542, BE138509, AV763026, AV763058, AA904275, AI521525, AA665330, BE077105, AA501461, AW969743, AW327591, AA535216, R94326, BF589824, AA574442, AW338179, AW271904, AI279417, AA651639, AI859946, AA524616, AW020150, AA833896, AV761862, AL042373, BE968744, AW004884, BF528591, AV760019,

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HDHEB60	39	499233	1 - 1407	15 - 1421	AL524364, AL527936, BE729676, BE734215, BG034535, BE879791, BG030700, BE782405, BG031399, BF219970, AW961043, AW245732, BE540977, BF125197, BE264862, BE264047, AA523441, BF348672, BF125434, AW250195, AW860381, AW246993, AI654715, AW168308, AI949310, AW068175, BE259690, AI393119, AW938768, BE279977, AW938746, BE857719, AW190234, AI871661, AA494392, AW900867, AA338903, BG006350, AL527587, BF091980, AA602247, BF804618, AW364083, AA357684, AW178944, R40832, BF374357, AW662637, AL524365, R42008, C20713, BF360339, BF915537, AW088134, BG035330, AI800433, AI559667, AI800453, AI536557, BE907440, AI689463, AI922091, AW151132, BF529043, AI285417, AI804505, AI952433, BF914091, AW118557, AI926593, AW151136, AI498579, AI539771, BE897632, AI432644, BG254284, BF304748, AI537677, AI494201, BF812963, AI500659, BG180468, BE883591, AI868831, AI866465, AI815232, AI866691, AI801325, BF812438, AI500523, AI538850, AW089221, BE968552, BE885490, AI887775, AI582932, AI590043, AI284517, AI923989, AI872423, AW172981, AI500706, AI445237, AI491776, AI289791, AW151138, BF811804, AI521560, AI889189, AI500662, AI582912, AW172723, AI284509, AI539800, AI889168, AI440263, AI538885, AI927233, AI866573, AI633493, AI434256, AI866469, AI434242, AI805769, AI888661, AI284513, AI500714, AI888118, AI277008, AI285439, AI436429, AI859991, BE964045, AI355779, AI623736, AI889147, AI371228, AI581033, AI431307, AI440252, AI491710, AI440238, AL047422, AI866786, AI567971, AI610557, AI860003, AI431316, AI242736, AI539260, AI828574, AI887499, AW151979, AL038575, AI539781, AI702065, AI539707, AI885949, AI285419, AW089557, AI559957, AI521571, AI469775, AI866581, AL047398, AW074057, AI815150, AI567953, AI446495, BE906230, AI867068, AI225248, AI698352, AI815239, AI371229, AI921420, AI624279, BF913616, BG252929, AI701890, AI687614, AA464646, BF038804, AI919345, AW858243, AI282249, AI962040, AI829330, AW078839, BE895765, AI554821, AI561170, BE764656, AI636811, AL515375, AI500146, AL042365, AW059765, AI263331, AI610756, AI440260, AI690946, BF814072, AI890907, BF811802, AW129310, AI866458, AI431238, BF815930, AI648567, BF925348, AL514069, BE540578, AA830821, AI924051, AI433157, BE964497, AI273179, BE621206, BG108452, AI371251, AI866510, AI499986, BE968711, AW151974, AW073697, AI866461, AI923046, BF339011, AI049859, BF752892, AI436458, BF526393, AI379711, AI918408, AI334445, AW169643, AL048403, AI915201, AA878808, BF764538, AI349814, AI953880, AI702902, AI800171, BE881675, AI819663, AI432656, AF118240.1, AB016531.1, BC000467.1, BC004356.1, BC000632.1, AK025906.1, BC004937.1, AK027081.1, BC007634.1, AL133070.1, X79204.1, AK000247.1, BC004908.1, AL080162.1, AL136781.1, AF017790.1, Z22828.1, U92992.1, BC002356.1, BC008382.1, BC001093.1, AL080127.1, AL136748.1, BC008195.1, AB048910.1, BC000713.1, AK024550.1, BC008818.1, BC001470.1, AK027116.1, AL133084.1, BC008488.1, AB063077.1, AL137275.1, AF056191.1, AK026086.1, BC004370.1, AB047609.1, BC003105.1, BC006164.1, BC002485.1, AL122098.1, AF111847.1, BC008893.1, M92439.1, AP001343.1,

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HDPBA28	40	106278 3	1 - 3433	15 - 3447	T27258, AU140225, AI634860, AI767588, BE536545, AV689583, AI991689, AI635347, BE386012, BE767008, AW976840, AI640606, BE178142, BE177971, AW502888, AA977785, AI979247, AW503911, AA971157, AL135446, T27536, AA491080, W74279, R07065, AI687230, T27535, AW816221, AA436906, BE151455, BF510035, BF803181, BE151443, AA152394, AW505067, BG003144, AA761110, AA377229, AV648450, BE671931, AI873792, AA397568, AA399529, AA679080, AI382296, AV648107, AV648212, AV648537, AI913234, AI741350, R50230, AI920850, AI018184, AA702114, AI244588, R81654, AI126673, AA152500, BG057181, AA148355, BE817269, AF222340.1, AF183569.1, AF106037.1, AB011097.1, AC008906.5, AC009073. 8.
HDPCL63	41	101900	1 - 3023	15 - 3037	AL040501, AL040502, BF312113, BF311401, BF312099, BF969955, BG118304, BE889750, BF528529,

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HDPCO25	42	460682	1 - 753	15 - 767	AI193249, AI809829.
HDPFP29	43	628254	1 - 1043	15 - 1057	AW575379, AA769318, AI796662, BG029535, AW269780, AA809133, AA427866, AW953923,

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HDPGT01	44	771583	1 - 2673	15 - 2687	AL524311, BG251269, BF310537, AU133126, BF683381, BF038290, AW732293, BF316433, AW170099, AI056333, BF349288, AA972732, AI675184, AW177595, BE141799, AW664330, BG056730, AW751928, BE141798, AU157403, AI803604, AW516199, AI421509, AI089433, AA622275, AU154510, AA699595, AW733094, BF838983, AI148225, AA921836, AA701632, AI361562, H75815, AV701643, AA931757, AA825979, BE837455, AI247022, AA035572, AI015040, AI032666, AW167576, T89750, BF349289, H06815, AI168573, AI702086, W42567, Z43621, AA505697, R92850, AI204070, AA724075, H06816, W72651, R93066, W76613, W42546, W86249, AW751931, AI272047, T16739, AI868745, AA860360, AI207229, AI249348, AI073394, AA035062, AA758712, AI204396, T11609, AA649046, AI168656, AA729782, AL110209.1, AL389957.1, AK001705.1, AB017494. 1.
HDPHI51	45	460679	1 - 714	15 - 728	AC005946.1, AC018755. 3.
HDPJM30	46	879325	1 - 1621	15 - 1635	AI420713, BF951818, R85260, H28149, BF899899, BF594396, AW292642, H44846, BF685411, AI739196, AI867313, BF063759, AI380559, BE504664, AW166357, BE735346, BF064117, AB001535.1, AP001754.1, AP001065.1, AP001064. 1.
HDPMM88	47	972734	1 - 4879	15 - 4893	AV715713, BF446914, BG057685, BF898163, AI083524, AI290271, AA318526, BF932901, R78174, C17785, R77809, BF898707, AW795715, AI638633, BF921994, BF904690, AW016805, AC025040.7, AK025125.1, AC016045. 8.
HDPOJ08	48	731863	1 - 1641	15 - 1655	BF968799, BF791555, AL513581, BE879926, AI949941, BE827843, BF968555, AI765763, BE875907,

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HDPPN86	49	103789 3	1 - 6283	15 - 6297	BE250002, BE394338, AW935469, AW749660, BG250570, BF982358, AI821271, BE541597, AI313180, BE293706, BE872198, W22478, AW976010, AI002815, AW963152, AU117456, AV762145, AV760760, BF792326, AW965008, AV764490, AW837083, AV700498, BG032943, AW600804, AV733710, AV759172, AA680243, AU123691, BE908796, AL037632, BE796439, AI076616, AW406162, AI732120, BF339640, AV700988, AA484962, AV699709, AW965642, AF074667, BE902459, AV760599, BG164166, BE273856, AI313166, AU118745, BE387734, AW961994, AA381195, AI364780, AU159301, AV761286, AA722372, AU158602, BE154495, AL044000, BG250302, AL041706, AL040921, AV700545, AU145083, AI817516, AV729960, AV760258, AW820787, BE071876, BF965477, BE071877, AW974126, AV759362, AI565581, AI284640, AI963600, AI608771, AL048626, AW440545, BF677892, AI204304, BE902975, AW317075, AA836811, AW088224, BF337291, AA634072, AI350211, AV704375, AV760777, AW193265, BF668217, AI133164, AV762395, BF736198, AW953071, AU157011, AW833862, BF241967, AL046409, AW995093, AV711987, AA491814, N94311, AI431303, AI963720, AW276817, BF828714, AI613280, AV762098, AA601355, BG249643, BF697673, AF330238, AV760937, AV728425, AW080939, AA599480, AV740801, BE156019, AI924251, AA469451, F36273, AV658688, BF055844, AI289067, AL119691, AV763354, AI061334, AV763971, BG058664, BF680074, AV725423, AL045053, AW970915, AW975425, AI471481, AI305766, AL138265, BE350475, AI679294, AA205915, AI754955, AL137737.1, BC001041.1, AK000310.1, AC010366.5, AC005280.3, AL137852.15, AC022148.5, AC004263.1, AP001666.1, AP001630.1, AE006463.1, AL354932.26, AC005484.2,

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HDPSP01	52	135228 0	1 - 2329	15 - 2343	BE876951, BF791762, BF112057, BG179551, AV752013, AI091429, BF001176, AV752703, BE391989, AI871101, AI458302, AW292744, BF196320, BE391322, BE390919, BF058297, BF435913, AI560217, AI808718, AI658996, BG056475, AI199318, AI381895, AI814608, AW190726, AA047000, AI479404, AI660983, BE388064, AA419038, AA035467, AW517227, AI361637, AI863893, AI198435, AI078128, AI093316, AJ403129, AA442664, AA725194, AI831358, BE206128, AI274339, AW297826, AW104389, AI948638, AI261248, AI869935, AA915909, AI283200, AI871060, AI269385, AI769275, AI200508, AI566171, AI275083, AI857306, AA910327, AA046943, AI291474, AI291805, AI983969, AW070742, AA423792, AW339900, AI308118, AI869944, AA012994, AI677732, AI913920, AA661657, AA427407, AI197804, AI141350, AA725186, AA954707, BF111675, AI864014, AI051823, AA864187, W24931, N41835, AA031475, N92812, BF734297, BF733728, AA035466, BF000025, AI026152, AA514348, R70380, AA961077, AA031617, AI673156, AA250784, AA378564, AW051192, AW452102, AA411122, AA886656, AW293787, AA012993, H91665, AA927216, AW149476, H91759, T86488, BC006411.1, AC022007.3, AC018809.4, X87479.1, Z22384.1, Z22374. 1.
HDPSP54	53	744440	1 - 3077	15 - 3091	BG256849, BG261011, BG178729, BG110345, AI923220, BE466885, BF667257, AW271504, AW243442, BE466659, BG171469, AV661528, AW271637, AW516811, N36059, AI804888, BE882420, AI650826, BF815232, AW964507, AI921747, BE936373, BF984751, BG259707, AI392784, AW076096, AI807747, AW103424, AA604757, AA633209, AW778887, AW418987, AW242326, BE622192, BF666519, BF978796, AW014203, AI925261, BF853590, AW131363, AW514756, N33223, AI819108, AI126250, AV649748, AI953896, AV714556, AI524472, BF697124, BE218100, AW629098, N21567,

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HDPUW68	54	812737	1 - 1734	15 - 1748	AW295848, AI132995, T48851, AI247571, AW469884, AV734061, T48852, BE378325, AW571432, AA344713, AW131386, AU138048, AW190967, BF896891, AA400508, AA400618, AA835515, AF170485.1, AJ007395.1, AJ130710.1, AF193441.1, AJ130711.1, AF227924.1, AB026265.1, AF247180.1, AF178981.1, AF223403.1, AF195092.1, AC020914.7, AF277806.1, AC011473.4, AF135027.1, AF310234.1, AF287892.1, AC008750.7, AJ130712.1, AJ130713.1, D86359.1, D86358.1, U71382. 1.
HDPXY01	55	879048	1 - 752	15 - 766	AW860154, AW860153, AW821875, BE869510, BF094022, BF337555, BF527692, AW845544, AW176604, BF734241, BF928740, BF360615, BE169703, AJ230819, BF734231, AL133649.1, AJ271791.1, AJ271790. 1.
HDTBD53	56	972757	1 - 2789	15 - 2803	AL521719, AL039239, AL522288, AL521718, AW850549, BE745185, BG036401, BF971064, BF982318, AV752274, BE410288, BF970662, BE179100, AA115485, BF037889, AI903708, W74580, AV752030, BF207332, AW069193, AW850706, BE260313, AA114996, AI147007, AA287865, BE294206, AA779902, AW953654, BF203424, AA287665, BF102950, AW089856, BE081349, AI424273, AI337872, W75992, AA039973, AW615357, AA287868, AA040007, AW207183, AW630077, AA844006, AI092051, AA035003, AW374784, W79563, AI095505, AI370765, C05140, AI961895, W92237, BF056098, AI431633, AA011411, AI381447, AA922567, AA688312, AI860011, AI200662, AA676566, H08173, AW590492, BG222429, AI741707, C02948, AA609401, AA427979, AV739012, H29396, AA453991, BE894938, H01836, BG165095, BF333733, W70295, BE242586, N41910, AA054984, R24822, AA156412, BG055899, H48740, H08272, AI241860, BE763810, T63735, R34728, Z42796, BE936536, W88710, AA367891, R36564, Z45070, AA412324, R78131, R56319, AA709055, AA429366, AI915050, AW673132, AL522287, R14984, AA347579, AW023366, AA853400, AA853401, W52589, AA476640, T39346, W88711, AI282590, T29951, AA411419, AA360166, T80320, AA331893, AI754899, AA602993, AA506382, R01609, AA328290, BF808365, N56432, AI832140, AW890834, T31756, R45735, BE929124, AA887981, W31306, BE710919, BE169167, AA039914, BF748450, AW381600, BF352203, AA648132, AI564214, R36407, AW374826, AA383447, T53688, AW198043, AA368172, T53689, N92423, BF237454, AA304402, D79323, AI905754, AA319927, AW197916, AW362124, AW579061, AW579502, AW751634, AA054622, BF086800, D25822, BF925479, BG054837, BF904194, BE966011, BE047833,

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HDTBV77	57	785879	1 - 2167	15 - 2181	BF689672, BE387282, BE898209, BE386984, AA393894, BE893192, W22615, AA134750, BG006306, AI769121, BG006608, AA808986, AA367857, AA344170, BG013403, BF368795, AA367892, AW605363, BG006302, BF932070, AW948496, AK027375.1, BC004282.1, AK027831.1, AK027849. 1.
HDTDQ23	58	130698 4	1 - 2193	15 - 2207	AI872206, BF966561, AW513884, AI912340, BE856991, AI758821, AW337178, BE327923, AW004890, AI572080, BG109128, AW058001, BF342854, AW886887, BF967940, AW474823, BF337371, BF591084, AA775261, BG164538, AA831357, BE087219, AW074361, AI361820, BF696525, AI982775, BF793075, AI690445, AA581345, AU156793, AI917776, D20022, AA825538, BF382552, AI360561, AW439592, AI798286, AI140796, AI277190, AA100279, AA485257, AA835492, AI522238, AW517943, BG035022, AI015234, AA706811, AI469550, BF197859, AI689240, AW265061, AI744762, AW450726, AI884872, BE714642, BE138867, T34498, BF213985, AW769512, BE073192, AA122332, BE138831, BF090537, AI811224, BG167993, BE932894, BF980823, AI355770, AA092467, AI471817, BE904497, BE719958, AI702026, BE171537, BG166879, AI597962, BG180321, BE171499, BF914841, BF967213, BE932875, AI681670, AA089786, BE327680, BE219939, BF032916, AU136610, AI624976, AK001917.1, AF035606.1, U58773. 1.
HE2DE47	59	619852	1 - 3519	15 - 3533	AL517387, AL526769, AL526907, AL523193, AL523194, AL515001, AL515002, BG030741, BF980577, BE903049, BE729941, BG163644, BE966268, BE067770, BE613706, BE780216, AL138389, BF196312, BG177870, AI041824, BE902470, BE384275, AI123426, BE384622, BE298710, BE067771, BE298416, BE885382, AI432657, BF966758, BF979153, AI708574, AI814491, BF036235, BF437789, AI720253, AI201638, AW182430, BF692903, BE867186, AA911185, BE748929, AW189237, AI432659, BE223052, AI687145, BF382011, BE564813, BG036747, AI024779, BE268867, AW029376, BF028837, AI024507, AW880654, N47923, AA706430, AA563625, AW662575, BG111471, BE748409, AA232692, AA864782, AI016478, BF676114, AW966708, AW958178, AW513800, AA010686, AI376397, AI081671, AA976495, AW167417, N98819, AA648548, AI721089, BF574678, AA311869, BF331286, AW731669, BE166594, W73934, BF110011, BF247329, BF382964, AA718927, N66559, BE832805, AA679466, AI224843, AA972211, W72314, AA664363, AI218733, AI571934, AA703942, AI690284, AW629428, N93202, AI350756, W28597, AA251850, AA688326, AA659803, AA143217, AA626686, BE614598, H96804, AW008436, BE693652, AA071465, AI041197, AA196284, AA010687, AA199756, Z30115, AW275267, N79354, N29375, AW151589, BF900837, AA935300, AA836130, AW673688, AW978790, AA777494, AW090055, AI090119, AW468015, R52190, T57886, AI992225, AW303565, AI364081, C18513, H64124, AA761409, AW024044, AA988587, AW511332, AW009882, AA332452, AA126237, BF816114, AA587628, AW674842, AI654600, H28730, AW519184, AA722914, AA568222, AA766768, AA452758,

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HE2NV57	60	740750	1 - 853	15 - 867	C05927, R72949, AA327984, AC084730.2, AC016673.5, AC004929.2, AC016716.6, AC008066.4, AC003969.1, AC024082.6, AC002302.1, AC013246.13, AC011490.7, AL158064.16, AC084729.2, AC078851.4, Z98743.1, AC020610.6, AF195953.1, AC016910.5, AL359394.9, AC005227.2, AC003692.1, AC016776.6, AC002300.1, AL451107.6, AL157838.24, AL031737.2, AL050335.32, AC007690.11, AC004541.1, AL022401.1, AC018796.4, AL358913.4, AL008583.1, AC005868.1, AL133383.10, AC006070.1, AC006211.1, AL359680.4, AL158035.14, AC087072.2, AC009424.2, AL391686.10, AP001684.1, AC006013.3, AL356461.15, AC016598.5, AP002980.2, AL158817.11, AL035685.21, AC034251.5, AC006134.1, AC020906.6, AL391241.21, AC015983.7, AP003470.2, AP001889.4, AL357519.19, AC087430.2, AC005081.3, AC005886.2, AC018509.5, AF277315.3, AC010913.9, AB020875.1, AJ011930.1, AL163300.2, AP000952.2, AL133387.8, AP000953.2, AL162503.12, AC025765.5, AP002342.3, AL445232.5, AC023114.5, AC004891.1, AL355792.8, AL163280.2, AL109662.3, AC010206.8, AL049843.18, AC017076.14, AC009362.8, AC005015.2, AL096791.12, AC002487.1, AC010726.4, AL353752.6, AP002846.2, AC005344.1, AC022363.24, AC009498.3, AP001699.1, AL138976.5, AC008064.2, AL357507.9, AP001670.1, AL137061. 12.
HE2PH36	61	570903	1 - 1544	15 - 1558	AA329666, AA664883, AL133353. 6.
HE8DS15	62	847060	1 - 2185	15 - 2199	AV725650, BE161426, AW130367, BF343057, AA127680, BF575221, AI096437, BF941499, W58383, AI161240, N95226, AW966449, AI356752, AI093508, AI057144, AA044288, AW130361, AI423547, AI221152, AI094774, H47283, AI352542, AI891136, AI002491, T53270, AA044116, R48378, R24320, AV658066, AI829703, AI819388, BE140169, Z44849, R16574, T39273, AA095159, Z25099, AW273857, R16633, AA384077, AI245095, AW026140, T93764, BE927909, N73937, AW118768, AA121543, AA995178, AI453845, AA703455, AI452494, AW044037, H40993, R48277, AW629019, T64039, AA904647, AW073189, W21055, AW263913, AI096938, Z28777, W03697, AW797518, AI039546, AI434419, AW050649, BG003285, AI240412, AA886341, H23905, AI695284, AI767991, H47284, AI309041, BE927916, AA724059, AI352281, AI584012, AA618131, AA357401, AI796309, BE936061,

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HE9HY07	63	420063	1 - 818	15 - 832	
HEOMQ63	64	603533	1 - 1322	15 - 1336	BG026315, AW102828, AI659843, BE551400, AI640582, BE208434, BF510823, AW955647, BE669917, AA789132, AA923523, W44769, AI346827, AI092608, BE267189, AW450220, AI350733, AW090676, AA830093, N98535, N69933, BF694104, AI000893, AI379944, AW968025, AA252680, AI202595, N32022, AL522177, AI026801, BF514413, AA075433, BG014214, AW452208, BE694426, BG171349, AI335272, AI634906, BE796712, AA846518, AA954350, AL522176, AI863776, BE265224, BF359220, BF359223, AW386074, BG112515, AV662306, AA973539, AA329532, F22685, AW136310, N28654, BG014217, AA610002, BG014216, C02160, W37089, N51549, AA361150, BC005984.1, AL109657.8, AL161659.17, AK025977. 1.
HEPAB80	65	130779 0	1 - 785	15 - 799	AW274007, AI677890, AW510786, AW468943, AA335322, AI807924, AW172560, AC006116.1, AC011506. 3.
HFABH95	66	566712	1 - 1333	15 - 1347	BF035708, AI431513, AA832175, AI251429, AV729905, AV754716, AI538491, AU122466, AI446474, AC005006.2, AC008747.5, AC008805.7, AL160155.19, AC005081.3, AC013751.6, AC006241.1, AC004216.1, AL137853.12, AC069285.8, AL590762.1, AC004491.1, AL035659.22, AL158040.13, AL022323.7, AL160411.25, AC005231.2, AC005952.1, AC008649.6, AC002059.3, AL355480.22, AC007850.29, AC024163.2, AP000501.1, Z98304.1, AL122035.6, AC008569.6, AL360227.17, AP000694.1, AC005480.3, AC009470.4, AC008392.6, AC011464.5, AC005911.6, AC008440.8, AC013734.4, AL034417.14, AL139082.18, AC005242.1, AP000511.1, AC008403.6, AC040160.4, AL353653.19, AP001725.1, AL049776.3, AC004148.1, AC007686.5, Z98946.15, AC007374.6, AL137787.11, AC000159.6, AL109984.14, AC002350.1, AC009087.4, AP000351.3, AF240786.1, AC005037.2, AC011490.7, AL022238.1, AC006101.3, AL356481.16, AC005971.5, AC010458.5, AC025588.1, AC005072.2, AL359091.10, AC008521.5, AC016831.1, AL117330.6, AC006312.8, AC007055.3, AC024561.4, Z83826.12, AF196969.1, AC002300.1, AL121891.22, AC005594.1, AC010319.7, AL022322.1, AL513008.14, AC008623.4, Z83838.2, AC005972.1, AC006084.1, AL117694.5, AC008119.6, AP001711.1, AC005102.1, AC004840.3, AL133174.15, AP002453.3, Z83844. 5.
HFAEF57	67	534142	1 - 628	15 - 642	AV655597, AW967329, AW963498, AV706016, AW966767, AL121984. 14.
HFCEB37	68	411345	1 - 788	15 - 802	AW971191, BE710287, AA493766, D56115, H06701, Z41729, AA285136, AA256963, F04210, AL118652, AW893768, AW893769, AW160783, AF258348.1, AC007552.4, AL050152. 1.
HFFAD59	69	520369	1 - 456	15 - 470	AV699250, AV662248, AV699269, AV719565.
HFGAD82	70	513669	1 - 1867	15 - 1881	AL119979, BF346635, AV726399, BF035097, AV727342, AL119977, BF920864, AW888751, N31682, AW148844, AA772781, AA326677, N23200, AW961610, BF976989, BE765872, BE765750, BE765749, BE765443, BF570590, BE765618, BF438771, BE766953, BE766490, F06586, BG057153, R60278, F07047, AA628815, AV722183, R16237, BF364146, AA204942, AV734361, N71200, AI000462, R54067, Z40722, BF337123, R54066, AW903171, H24278, AV726415, H16893, AW897545, H16783, H22887, R16238, F03521, R42035, F05678, T80483, AA321847, AV731162, AV731097, AV730504, AV730299,

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HFIUR10	71	532060	1 - 527	15 - 541	BF195618, AA191239, AW969824, AA009856, AW019964, AA808036, BE677291, AW973259, AW023662, AV742957, AU146063, AI369580, BG109444, AU153717, AV709074, BG032605, AI357823, AW888719, AL110373, AI832009, AV708388, AV725797, BE150580, AA223512, AV734980, AA402529, AA595661, AW410201, AA683069, AA191418, AI144036, AW474168, BF681348, AI590458, AI590499, F08248, AW302048, AV760508, BE794962, AA665181, H07953, AW971071, AA654781, AV763410, AA749035, BF965290, AI609972, BF676985, AV708385, AW504485, AV762633, AW166808, AA282951, AI860535, AI792575, AA634889, AW302950, AL048060, AI254913, AW875172, AI281689, AA668587, AA084619, BF675051, AI354423, AA832077, AI733129, BF674550, AL041924, BE139451, H73550, AA828853, N39953, AW863393, AV757526, AI859946, AW976008, AW023111, AA747234, AI565084, AV710482, AW814024, AV710045, AW963482, AI355246, AA814925, BE077105, AA653182, AA664521, AW440305, AI054397, AA651639, BF725761, AV758073, H15652, BE280771, AW438542, T74524, AW191063, BF940118, AW968205, AV762973, AA552578, BF965924, BF879045, AI251034, AI251203, AI251284, AW805539, BG236628, BE878259, AI250552, AA632556, BF809041, BG029224, BF868994, AW020736, AF236698, BE139139, AW271904, BF978025, BF681424, AU118374, AV758790, BG110480, AI803809, AV758097, AA574442, AV733434, BE155302, AA644664, AI792521, BE246472, BE901278, AA626825, AI686913, AV706237, BE155299, AW302293, AV702609, AA533123, BE968477, AV738383, BF814446, AI891080, AA516190, AA533040, AI284543, BE273825, AW779609, BF525663, AI380617, BF914419, AL079734, BG166965, AW069227, AL043351, AI267161, AV762870, AV658819, AV709273, AL042735, AA503018, AI973173, AL046746, BE062357, AI963705, T69857, AV730245, BF810071, AW301736, Z97987.1, AC020913.6, AL031281.6, AC007637.9, AL096757.1, Z93017.6, AC087225.1, Z83840.7, AC008073.4, AF245699.1, AC010349.7, AC087315.21, AL163011.3, AC004106.1, AC004132.1, AC008925.3, AC004990.1, AL133351.33, AC010618.7, AC006275.1, AL035405.10, AC034203.7, AC006930.1, AF156495.1, AC008754.8, AP001732.1, AL139824.22, AC003037.1, AP001646.4, AC005162.1, AL050341.18, AL034420.16, AC024075.4, AL117382.28, AC008521.5, AP001039.1, AL512378.7, AC005778.1, AC091394.2, AL132768.15, AL139385.12, AL049569.13, AL109914.16, Z95152.1, AL163541.13, AC006367.3, AL442203.12, AC005684.1, AL117377.18, AL109828.22, AL031681.16, AC007488.15, AC007425.16, AC018462.4, AC007934.7, AL078602.13, AC010002.6, AC005038.5, AC009743.1, AC006538.1, AC053467.1, Z95115.1, AP001922.4, AC010203.13, AC010150.3, AC006545.3, AC006546.9, AC004970.2, AP001696.1, AL390736.6, AC003035.1, AL355543.13, AC007318.4,

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HFTBM50	72	545012	1 - 748	15 - 762	AL529436, BG254023, AA069656, AW512689, AA928735, BE901109, AL529437, BE074967, BE074973, AA423996, AI027673, AI130940, AA827360, AA424006, AA421599, AW602733, AI580837, AL526924, AA114876, AA576953, AI858981, BF222157, AL526960, BF542049, AA136831, AI200715, AI358322, AA988755, AW602739, AA187921, AL527090, H10340, AI499041, H10044, AA252300, AA188494, AA856927, R44331, AA588683, AW364266, BE092940, BE007334, R51006, AI253378, AA481649, AI686745, AI628242, BE092920, BF733881, AA729977, BF026424, AW804569, AA421594, AW994967, AA481416, BE733257, BF876214, AA679567, AW028221, AU134538, BE251492, BE729280, AI906091, BC002480.1, AK023414.1, AP002347. 3.
HFTDZ36	73	545726	1 - 1089	15 - 1103	AV721599, BF732420, BF510533, BF508158, BF508241, AI638188, AW181935, AI758929, AW592730, BE967495, AA447514, AI078837, AV723652, AI218418, BF692673, AA884756, AI335250, AW118870, BE044339, AA426363, AV730822, AI868197, BF947599, AA927228, BF952754, BF952302, BF952504, AW905268, AW905266, BF952591, AI673798, BF952850, BF952505, AW905263, BF952750, BF952589,

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HFXBL33	74	778070	1 - 1619	15 - 1633	BG141322, AV652809, AV662223, AV699247, AV699167, AV662247, AW963961, AV699098, AV662272, AV725496, AV727824, AV699218, AV719825, AV719156, AV699200, AW952432, AV720062, AV720893, AV653163, AV650903.
HFXJX44	75	701988	1 - 1370	15 - 1384	AC004491.1, AC024579.4, AL136084.11, AC016564.5, AC005015.2, AC007011. 1.
HFXKT05	76	658690	1 - 1701	15 - 1715	AU124431, AW960435, BF525944, AA781090, AW514159, AW390483, AW965129, AW170237, AW582015, AI700395, AI079309, AW339256, AI140441, BE700940, BE842726, BE842730, BE700936, BE700869, AW581975, AI022857, AI903097, AI401014, AI379419, BE700861, BE700862, BE772035, AI434349, BE772040, BE772042, AW673336, BE700873, BE700876, BE842723, BF439588, BE700941, BE700945, BE700943, BE772099, BE700938, AA703354, N50989, BE772066, BE700937, AA719006, BE908235, BE772053, BE772081, H69547, BE700904, BE772059, AA574083, BE830929, BE772082, BE818955, BE818958, BE772101, AI251845, AI243536, BE772019, BF870875, BE818964, AW517983, BE700851, AI983670, BE772020, BF359589, H70004, AW820559, BE840628, BE700898, T63151, BG012510, R11344, AA305705, BE818962, BE840434, BE840457, AW752129, AA565124, BG010792, BF849721, BE772047, AI905362, AA731490, BE818915, BE772087, BE772018, BE772074, BF110884, R14845, BE772086, BE772015, AI983820, AA344670, AA889063, R07438, BE840445, C15468, T63006, BE170135, R09631, R06659, BE772017, BE836162, AI540442, BE830923, AI023272, AW868068, BE830919, AW868069, BE818892, AA324635, AW960971, BE818951, AW674579, BE832289, BF091071, AK001249.2, AB007936.1, AK027078.1, AL117402. 1.
HGBHI35	77	570262	1 - 1423	15 - 1437	AW027617, AW167655, AV705616, BF112047, AV647323, AI761852, AV647362, BF475491, BF941241, AU134617, AW273477, AA632135, BF589834, AW188958, BE328783, BF673582, AW025350, AW469123, AI248475, AW071025, AW513405, AV707439, AA443956, AW959532, AA974499, AA586906, AA411210, AA748561, AV647324, AA574049, BF001545, AA993212, AU155540, AA405832, AA418055, T65000, AA633212, AA417996, AA716696, AW338423, AI951713, AW269824, AA705781, AW294610, N29931, AW193961, W74344, AI623473, W95062, N58311, AA434443, AI452555, AI476814, AI707848, AI591113, AW071570, AA504192, AI284330, AA993753, AA422102, AA814543, AA833607, R59175, H69589, N27730, N27744, AI050821, H91466, AV661353, N26927, AA384582, T53881, AA723025, AW952885, AA708478, AA412129, N80150, AA805411, AA325056, H86073, AW080735, AA719996, H48787, AW439101, AA327279, AW439110, R72184, AA317298, AA290758, AI302593, AI041429, AA932990, AV692965, H68481, AA290757, AI301278, AA928847, AV709914, R70407, AA342345, AW971285, T71152, AA528307, R00838, AI915200, AI470398, AA888272, T50944, T54028, AI784177, R69430, AI298655, AI801093, AA363967, AA935078, AA935062, T99499, AW450038, F37718, AI470409, AA419235, AW074842, AA700546, BF057503, AV656088, AI798643, AA946561, AV684912, C05231, AA342344, AA405831, AI682312, R72230, AV696820, AI557037, T72850, BG122003, AI478342, AA504193, AI474859, W91943,

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HGLAF75	78	566838	1 - 762	15 - 776	AW968403, AW268460, AV699333, BE388094, BE387809, AA805707, BF112044, AA769677, AI379717, AI419895, AI858342, AI708860, AA044030, AA465222, AI677780, AI189447, AI221144, AI073526, AI286149, AI540808, AI298414, AA847808, N29749, AW170779, AA344901, AA044352, R52970, BE836466, BE716265, BG057223, BE836496, H40701, R55340, AA873679, AI363753, BF792412, R40137, AW965142, AA725486, AA344902, T27542, BE716174, N57171.
HHENV10	79	562772	1 - 1141	15 - 1155	AC004912.1.
HHGCG53	80	340818	1 - 393	15 - 407	
HHGCM76	81	662329	1 - 697	15 - 711	AW248957, BF828801, BF828604, AI675194, AW028119, BF826770, BF827069, AW452880, AI491913, AI799880, AW450970, AI377883, AI201976, AA595164, AI088096, AW612440, BE792795, AW006952, BF063362, AI697133, AA643065, AA580017, AI819005, AI866931, AI560641, AA635584, BF446220, AI829011, AW952316, AL524066, AW243832, AI200458, AI634449, AI670745, AI269568, AA326815, AI873666, AL523219, AL520944, AI478177, L31980, AW245254, AW194690, AW771866, AI767850, AW079488, T87766, D45523, BE242113, AA055697, AI306732, AW275312, BE280419, AI908657, R48473, AA013188, AI908646, BG250796, BE796614, T72628, BC002980.1, AC003665. 1.
HHPEN62	82	695134	1 - 2138	15 - 2152	AI939620, AI480056, AW300615, AW300620, AI589129, BE386438, BF920454, BE386547, AW961851, AI911546, AV726263, AI361251, AI498527, AV725146, AW901919, BE967591, H41544, AA326679, AA348503, AI422476, AA912288, AI423129, BC004271. 1.
HJABB94	83	456466	1 - 1541	15 - 1555	BE905356, AI026821, AA503776, BF114724, AI435527, AL036946, AW298357, BF240642, AA969442, AI767392, AI142574, AI094514, AW073866, AW241144, AA206595, AA040034, AA354909, AW972134, AA814156, AA933895, AA040828, C01416, AA457220, AL138875.8, AY027525. 1.
HJACG30	84	895505	1 - 1518	15 - 1532	AA311188, BF940968, AI478697, AA309875, AA481249, AL533052, AA481563, AW242463, AA760629, AV651897, AV660258, AV661286, AV709580, AV653353, AV726590, AV703632, AV725255, AW960067, AV705453, AV726243, AV652001, AV704144, AV726194, AW956292, AW949777, AV708520, AV727618, AW959858, AV656283, AW967329, AV727932, AV728953, AV725582, AV708786, AV708872, AV661369, AW952013, AV705340, AV704234, AW965148, AV726156, AV705836, AV708991, AV725618, AW952301, AW958796, AV725596, AV709248, AW959986, AV726337, AV709407, AV728355, AV725031, AV707948, AV725441, AV729424, AV652528, AV725577, AV707556, AV704626, AV702071, AV706223, AV705665, AV704785, AV728404, AV709733, AV729366, AV708320, AV705343, AV727822, AV707264, AV704611, AV729473, AV702738, AV725321, AV690930, AV728743, AV727978, AV727337, AV727562, AV729129, AV704712, AV701953, AV727052, AW955629, AV729532, AV704520, AV706964, AV704973, AV702817, AV705504, AV709356, AV704279, AV705829, AV702164, AV701880, AV701626, AV707401, AV704756, AW955019, AV701183, AV728289, AV708203, AV703591, AV697880, AV647941, AV703417, AV753624, AW963446, AV654035, AV709935, AV726628, AV707654, AV706290, AV655552, AV654282, AW949521, AV709880, AV709939, AV705189,

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HJBCY35	85	719729	1 - 1545	15 - 1559	AL518865, AL526445, AL518864, BF690211, BE795952, BG261247, BG122941, BE871131, BF342499, BF797882, BG034854, BE874386, BF684303, AW958340, BF055513, BE265238, BF055496, AL042954, AL044311, AW393087, BF590235, BE251517, BF688851, AW500006, BF750912, BF436031, BE207255, AI523943, AI809559, AW615714, AI088845, AI199469, AI088821, BE792741, AA707004, AI393362, AI859578, AA864359, AI359119, AI963339, AA259086, AW027379, AA186786, AA703021, AA305929, AA393356, BE729570, AI961726, AW274049, AI216448, AW503180, AW505339, AI015694, AA291342, AI049539, AW873566, AI092749, BE410341, AI817912, AI870620, H44330, AI366215, AA258242, R46300, R16949, AI744596, R54656, BE386449, BE410337, AI807057, AW081887, AL041401, H15972, BE710574, BE410414, BE535502, BE222788, AA398688, AW273864, AA404987, D59795, AA077661, BE047327, T10451, AI871075, D59810, AI368575, BF526818, AA962247, AA335735, AW000813, BF435172, AA188015, R75708, AA329264, BE713106, AI218840, AA329538, AA291343, AA826970, T35806, R10855, D59833, D59821, BE547124, D80231, AI080034, AA299767, BF203222, AI908002, AA973311, AW087244, BF920764, AI648592, D80329, BE537114, BF511965, D59677, W93021, AI919083, AA749327, R16895, R55419, AA354448, AA136776, R54853, R46205, D59561, AI969256, W51754, AW273865, R10856, AI452772, BF765954, R10335, BF858687, AA076725, BF955782, BF206768, BF310354, BF032473, C01203, BC004286.1, AL050110.1, AB037861.1, AL137358. 1.
HJPAD75	86	651337	1 - 1217	15 - 1231	AL530365, AL524811, BG035149, AL524846, AV653215, AL525028, BF031163, BE464161, BF064198, BG057645, BE677690, AV714679, AI954819, AA708718, AA773040, AW206827, BE677490,

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HKABZ65	87	862030	1 - 1175	15 - 1189	AA715814, AA503019, AV762033, BE155099, AV734997, BF917346, AW338860, AC011666.28, AF242518.1, AF109907.1, AC004867.5, AC020917.4, AC004166.12, AL356915.19, AC005071.2, AC004878.2, AC005052.2, AC005081.3, AC002549.1, AL590763.1, AC020663.1, AC006064.9, AC008745.6, AC004858.2, AC022405.5, AC007666.12, AC008750.7, AL451144.5, AP001716.1, AC009131.6, AC004656.1, AL109825.23, AL355312.24, AL035086.12, AC010605.4, AC004067.1, AC004477.1, AC008736.6, AL109915.10, AC006023.2, AL033529.25, AC007637.9, AL139317.5, AL031311.1, AL049776.3, AC004971.3, AC009220.10, AL080243.21, AC005015.2, AC004686.1, AL022318.2, AC002310.1, AC009123.6, Z93015.9, AC021999.4, AL355353.23, AL050318.13, AL161756.6, AC011464.5, AL132712.4, AL359513.12, AC007546.5, AP001695.1, AL035683.9, AC018711.4, D87675.1, AL133444.4, AL139100.9, AF030453.1, AC006077.1, AC008895.7, AP001713.1, Z84487.2, AL357153.4, AL163636.6, AL359382.23, AC004770.1, AP001972.4, AC004675.1, AL355392.7, AC020906.6, AL138784.30, AC020754.4, AL162426.20, AC002288.1, AC009068.10, AC008101.15, AC008623.4, AC008891.7, Z98884.11, AL136137.15, AC011247.10, AL133163.2, AP001727.1, AC005098.2, AC004659.1, AC005670.1, AL139022.4, AC009812.17, AF088219.1, AL035404.20, AL139801.17, AF228703.1, AC002492.1, AC006084.1, AL353594.13, AC005077.5, AL160271.19, AP001724.1, AC008537.5, AC024561.4, AL139353.3, AC004491.1, AC008626.5, AL391987.15, AC010530.7, AP003352.2, AC009267.15, AL122013.5, AP000008.1, AC087071.2, AC009314.4, AC020913.6, AL078463.11, AL096700.14, AC002369.1, AC010102.3, AP003357.2, AL031123.14, Z95331.2, AL513008.14, AL118501.22, AP001435.2, AC005200.1, AJ400877.1, AC011469.6, AC016772.8, AC005089.2, AC005088.2, AF312912.1, AL022316.2, AL080317.11, AP001693.1, AP000553.1, AL390294.19, AC006345.4, AC091394.2, AL359813.23, AC007283.3, AL353807.18, AL109921.21, AC074121.16, Z98742.5, AC007383.4, AF243527.1, AC027130.5, AC010504.7, AL035462.21, AC010650.8, AC005180.2, AF334404.1, AL139187.19, AC005037.2, AL021391. 2.
HKACB56	88	554616	1 - 482	15 - 496	AI935239, BE122852, U51140, BG121875, BF970449, BE879967, BE545287, AI311480, BF968910, AI207454, BG031442, BF815930, BF792050, BF339322, AI924051, R99209, AA669025, AA505147, AA806160, AK026797.1, BC000650.1, AB060839.1, AL133557.1, BC009192.1, AL136622.1, AB048888.1, AL512754.1, BC002485.1, BC004908.1, AF004162.1, AL358532.11, BC004181.1, BC006251.1, AK026603.1, AK000647.1, AK024974.1, S69510.1, BC008823. 1.
HKACD58	89	135220	1 - 3139	15 - 3153	AL528271, BE513051, BE874633, BE727126, BG119953, AA877796, BE897630, BE616928, BE873485,

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HKAEV06	90	135226	1 - 2482	15 - 2496	AU133136, AV762150, AW967049, AI114751, BF678978, BF698605, BE536006, AA317243, BE748143,

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HKISB57	95	625956	1 - 1478	15 - 1492	BG253059, AI888563, AW083174, AI890983, BE677527, AI742994, AA581853, BE208188, AA496043, AI749573, AI433172, AA912116, AU152415, AU151244, AA526295, W72233, AI708515, AA029171, AI289783, AA147482, AW001857, BE744941, BF851250, W76470, AI148076, AI619715, W32695, AI973179, BF856405, AA086231, AI536682, AI244167, AW205328, AA112137, AI015550, AI159953, AA449234, AA449289, AI886087, R48602, AW974749, R48705, N57904, W73612, AA515533, AI095398, AA086322, AA554446, AA317019, BE019888, R07096, AA894669, AA112027, T96414, AA923651, T96497, AI581984, AI093238, AW084446, BE834394, T65129, AA100811, BF767404, AA652428, W32694, AW364698, BF371383, AW390788, AI903419, AI903380, AI903350, AA300051, AW886927, H55267, AA029067, AA588851, AA588463, BF931116, BE646329, AW514396, T65909, AW578218, AW800794, R07042, AA625855, AA663955, AA687595, AI581808, R76016, W22074, AA043407, AA436950, H39017, BF814527, AI824576, AI702073, AI698391, AW080090, AI633062, AI608936, BE786043, AI358213, AI306705, AW983832, BE963838, BG179993, AW051258, AI677796, AW051088, BF856017, AI932794, AI366900, AI352497, AI889189, AW983829, AI270183, AW163834, AL514731, AI434468, AI812015, AI249877, AI679672, AW118518, BF812960, AI284131, AW029611, AI468872, AI699011, AI927755, BF792961, BE966388, AI886753, AW827289, AI564719, AV743962,

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HKMLM11	96	514788	1 - 940	15 - 954	BG036576, AW376266, AW024675, AW965560, AA946948, BE834077, AA306783, AV738527, AV739697, BF241514, AV740463, AA758808, AA431001, AA910368, AA336054, AA335971, AW237846, AW827285, AI050666, AV755459, AI583054, AA764946, AA459982, AI811603, AI683160, AV734888, AV721366, AA648361, BE397723, BF970114, AI336575, BF306639, F37462, AI872164, AV694812, AW301344, AA830333, AI633321, AA678887, BE876047, AV706721, AA563942, AI245332, AA653346, BE740632, AI360195, BG177101, BG026443, AA437293, AV698290, AV706279, AI933756, AW102858, AW022121, AV656973, AW582932, AW238753, BG110384, AI345143, AI224463, AA836317, AL047398, AL041154, AI814841, AI621106, AI436429, AI364620, BE620084, AI343119, BG109221, AA100151, BF796402, AV760181, AI349012, AI627692, AA765010, BE885490, AW021373, BG033906, AV756956, AV764180, BE011885, AI559654, AC005551.1, AF217998.1, U91329.1, AK026600.1, AF197929.1, AL137555.1, AL133093.1, BC007797.1, AC004227.1, U68233.1, AK027114.1, AL359583.1, BC007534.1, AL137662.1, X86693.1, BC002688.1, BC004145.1, AF217991.1, AK025549.1, BC005094.1, BC008196.1, BC006147.1, BC007280.1, AL512746.1, AK000632.1, BC000007.1, AF111112.1, X53587.1, AL136816.1, BC006481.1, BC001128. 1.
HKMMW74	97	581399	1 - 1780	15 - 1794	AI524360, AA582463, AW970030, AW088049, BF845261, AV744082, BG166773, BF970654, AL137859.3, AC008784.6, AC022382.3, AC079844.3, AB038490.1, AC007917.15, AL158070.11, AL136231.12, AP000555.1, Z96074.4, AC006430.22, AP001695.1, AL354811.13, AC078958.30, D87675.1, AL138849.12, AC004019.20, AL391415.12, AC079950.23, AL117694.5, AC004935.1, AL121834.20, AL109921.21, AC008551.5, AF200465.1, AC008892.5, AC068799.14, AC006036.3, AC005725.1, AC015982.9, AL391262.3, AC004104.1, AC005079.6, AL132988.4, AP000692.1, AL590116.8, AL158144.15, AC005305.1, AC003049.1, AL022313.1, AC005520.2, AL353135.32, AL117377.18, AC025887.4, AC004468.1, AC083876.2, AC004774.1, AC004634.1, AL121900.26, AC034198.6, AC006460.3, AC005522.2, AC018828.3, AC067742.5, AC022383.3, AL161655.8, AL445686.14, AL031224.1, AP000128.1, AP000206.1, AL021154.1, AC009006.6, AF111167.2, AL589782.7, AL590785.7, AC021016.4, AL133387.8, AC006115.1, AC026439.3, AL034394. 2.
HLDON23	98	636083	1 - 1248	15 - 1262	AL529086, BE904120, BF337766, BF345489, AV706125, AI681123, BF002270, BF055322, BE856092, BE305227, BE219427, BF438375, BG149525, BF057786, BF590112, BF196165, AI741848, AI636347, AI973055, AI554720, AI871117, BE220195, AI745311, AW192924, AW340966, AA706712, AI091179,

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HLDQR62	99	753742	1 - 2558	15 - 2572	BE876197, AU133975, AW170131, AV723948, BG178057, AV652458, AW836234, AW608052, AA047046, BF104746, AA486037, BE395776, AW385580, AA488655, BE699041, AA932253, BG104619, BF671350, AA854943, AA418105, AA829456, AA243385, BE699051, BE936060, AI346694, AA418007, AA503398, AA053835, AW067836, AA878478, AI309218, BF820483, AA287990, W37960, AI401102, AI279485, W37900, AI423510, AA610711, AI050735, BF939011, BE699047, AA701403, W30974, AA017371, AW385388, AA911160, BF928600, H10281, W32542, AA133579, AV721259, H81907, BE908122, H11712, AA657490, H09562, R97956, BF810354, N68428, BF841567, AA018681, BF810349, AW838671, AW274397, BE699044, BF737894, H17436, AA133578, T03483, BF529092, BE699011, R93915, T84200, H10225, R97955, N91220, F09018, BE244933, BE697384, AW474873, Z43397, AA677745, F11358, AW838680, Z42508, H08994, H11779, R18755, AW067888, H86384, R20010, R44826, T78746, BE546845, BF768165, AA676360, Z41104, R12303, R61069, H80952, H01770, BF362799, AA857228, BE092626, AW361033, BE246721, R12953, F11514, AA298600, AA233314, H82000, Z45386, AA047038, AA988879, AA776420, R61792, BF925722, F02025, H37922, AA946813, AA058662, BE793798, AA298811, AW954042, AI024907, AA515707, AA579408, C02381, H38137, H80857, AA190438, AA059270, AW953912, W32541, AI253018, BF755527, AA252608, H39230, BF087406, BF841077, BE699066, F09175, AW608049, R36072, AW607934, AW242636, F02790, AA018740, BE092426, N47523, AW951415, BE872758, AA670010, BF793691, H86054, BE699208, AA017201, AA059226, BE857637, BG011131, AA233315, AW169463, BE935974, AA910836, BF756516, AA504287, AA489248, AW452612, BE858890, BE699076, AA953019, AA191764, BF930488, BE746764, AA552521, BF932022, BE080981, AW385586, BE092405, BE047109, AW838675, BE074538, AB046801.1, AC026749.5, AC026437.5, AC010491.3, AK001799.1, AF274753. 1.
HLDQU79	100	740755	1 - 1474	15 - 1488	BG256275, BE867624, BE907396, BE855521, BF034422, BF530803, AW959247, BE782005, AI126689, AL121446, AA757065, AW630129, BF768037, BE746763, AA206154, AA460401, AI276320, BF998689, AA295243, BE242732, BG035901, AL040350, BE242810, T86168, BF983867, W05088, AA347337, BG252443, AI133502, AF064093. 1.

HLHAL68	101	684216	1 - 690	15 - 704	AA359084, AC018797.4, AF224669.1, AF283321.1, AC007883.3, AC006038.2, AC034251.5, AC006345.4, AC008149.14, AL355392.7, AC006057.5, AC084864.2, AL354720.14, AC084865.2, AC006435. 7.
HLIBD68	102	778073	1 - 1008	15 - 1022	AL538046, BF975484, BG260893, BF062040, AW250850, AW954319, BG118275, AI633756, AI436560, BE646174, AA975057, AW302253, AI651397, AI825665, AI479926, AI635567, AI612806, AI640598, AI653427, AI248825, BF770160, AI333221, AA609320, AI916748, BF346659, AW001438, BF941021, AA397893, AI083783, AA399663, AA302889, AA484860, AI659648, BF222019, AI692578, R49550, AW016187, AA393712, AI673346, D80738, D81106, D81495, D81643, C15479, AI696498, C15522, R42643, AI761655, AA302888, D81794, D81487, D60344, AA302884, AA302883, BF813253, AA091824, BE743563, N49704, AI476597, D81533, N87760, BE396027, AA352126, AA281538, AA280240, AL133447. 1.
HLICQ90	103	791828	1 - 1752	15 - 1766	BF980403, BF726329, AI984197, AI192533, AI559494, AI378638, AA430026, AI061413, AW172705, BG165333, AI190915, AA430235, N62729, AI689890, AI360764, AA705532, H90333, H30177, T99745, H78217, T86019, H26993, T91236, AV645894, AA330598, N75483, H42449, BE766728, AW135351, AA976652, AA383620, BE220880, AI630095, BF381551, BF767606, BE087130, H42847, W05293, AA911697, AI659925, BE766726, H82733, T99746, BF889067, AW955970, AW971740, AI432644, AI431328, AI623302, AW968355, AI431347, AW972091, BE672759, AI432653, AI431230, AI432654, AI432655, AI431310, AI431312, AW081103, AI432677, AW968356, AI431323, AW972093, AW968729, AI431354, AI432661, BE672719, AI431307, AI431316, BE672732, AI431337, AI432650, BE672745, BE672748, AI431238, AI492519, AI432675, AI431350, AI431231, BE672767, AW972092, AI432651, AI432647, AI431243, AI431330, BF448552, BE672742, AI432662, AI431248, BE672644, AI432657, BE672774, AI432649, AW972090, AI791349, AI431257, AI432665, AI431247, AI431318, BE672738, BE672792, AI431235, AI431321, AI431315, AI431246, AI432643, BE672743, AL042519, BE672640, AW129223, AL042931, BE672622, BE672627, AI492510, AL042729, AL042832, AL047611, BE672754, BE672626, AL043295, AL357075.17, AF064854.1, AL133082. 1.
HLTHR66	104	699812	1 - 2272	15 - 2286	AW978874, BF507862, BF033134, AL135232, AI673052, AW612437, AW880652, BF508030, AW118937, AI912990, AI651420, AI754531, AI285856, BF431306, AI760176, AI805972, BF511821, AI123209, AW001864, AI377932, AI141443, AI743946, H19020, BE857717, AW962968, AI221575, AA588506, BF475287, AA026012, AI249502, AI660528, AI949710, R68887, AV653095, AA026000, R77684, H19313, AI460280, AA829761, AA357748, BF511571, R77685, BE671786, AA084602, AI687732, AW889295, BE002919, AI812062, BF365444, C21025, AL136231.12, AF147395. 1.
HLTIP94	105	108733 5	1 - 1226	15 - 1240	AA552985, AA314716, BE778519, BE894256, BE779796, AA228139, AI802948, AC005325. 1.
HLWAA17	106	629552	1 - 983	15 - 997	AL522002, BF305304, AL521608, BE732838, BE899550, BF344719, BG115015, BG109203, BF982386, BE410162, BE735023, BE901175, BG117962, BE281306, BG165427, BF793440, BE901577, BE872442, BF316646, BE409982, BF982251, BF970528, BE262711, BE299415, BF340859, BE386152, BF569778, BE281612, BF305644, BG251248, BF673757, BF183244, BE547252, AL521166, BF237978, BG249255,

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HLYAC95	107	778075	1 - 298	15 - 312	AV764526.
HMADK33	108	561941	1 - 850	15 - 864	AL538273, AW139111, AA663592, AI582741, AL120259, H51572, AI122619, AI124509, BF366373, R86660, H50906, R86835, BF836623, BE884648, AF070673.1, AF030196.1, AL161976.1, BC005837. 1.
HMAMI15	109	135240 6	1 - 1244	15 - 1258	BE790239, AI114496, BE047613, AI609021, AI478544, AI949665, R96283, AI205799, W39248, AI670908, T70976, AA070919, AI243978, AW854183, AI796472, BF883407, AW975683, AA654405, AI125888, AA730911, AA545731, BE222003, AA730927, C21177, AA721678, AI478489, AL137139.9, AL139035. 27.
HMCFY13	110	635301	1 - 869	15 - 883	BF026299, BE277091, AI343297, BF027218, BE390121, BE387283, AL514638, BE388858, AI364111, BE389119, AI668959, BE391988, AW206551, AA676232, BE870993, BF002101, BE277034, BE729557, BE276352, BF125430, BF896609, BE386944, AW207225, AA551687, BE718320, BF131318, AI990714, BE693868.
HMDAB56	111	560676	1 - 1451	15 - 1465	AI075053, AW972336, AI199257, AA493693, N80663, AW879550, AL138455, AA633753, AA640410, AA640430, AW815064, BF820510, AA018283, AL037554, BG033220, BF822854, AV759329, BG033926, AL120343, BE062169, BF679557, AV757425, AI631355, AW129526, AV710289, BF868399, AW063373, BF437493, AW936354, AI094787, AW500029, BF915002, AA908411, AV760207, AV761925, AW975971, BF666395, BE858219, AV764035, AU137841, BF679274, BG002515, BF698704, BE064275, AA493136, AI700109, BE883107, BF699964, AI918465, AA507547, AI805123, AP002088.2, AC008014.5, AC009470.4, AC011450.4, AL133480.9, AL356244.12, AP000493.1, AC008521.5, AL353741.16, AC004638.1, AL139148.11, AC011475.6, AL158832.13, AC004634.1, AC005102.1, AL135749.3, AC010105.12, AC000088.2, AC019197.7, AL133214.12, AP000901.5, AC008891.7, AC021188.6, AL049776.3, AL117355.5, AC002128.1, AL450483.1, AC007774.1, AL080315.18, AC008622.5, AL135901.23, AP001692.1, Z84485.1, AC007097.4, Z84480.1, AC022415.5, AC008747.5, AC000082.4, AC020908.6, AF121897.2, Z98747.1, AC010422.7, Z84720.1, AL109921.21, AC090944.1, AC074338.1, AC007318.4, AL136219.17, AC004841.2, AC003109.1, U82668.1, AC003103.1, AC020977.5, AF057280.1, L44140.1, AC004774.1, AC011242.8, AC020913.6, AL354935.23, AC069080.12, AL389888.8, AC007036.3, AL136359.13, AC005746.1, AC006441.13, AL133453.3, AC084732.1, AL353194.13, AC004466.1, AC004253.1, AC025165.27, AL160175.5, AC005840.2, AP000251.1, AC007225.2, AL161779.32, AL033378.12, AL359397.3, AL022725.8,

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HMEED18	112	560775	1 - 1355	15 - 1369	BF967947, BF794640, BE744676, BE872383, BE261972, BF680443, BF967220, BE732377, AI417193, W95515, AW294641, BF306808, AI189166, BE856708, BE644954, AI949989, BF530795, AA628537, BE551422, BE747031, BE304795, BE735201, AI457735, BE870962, AI634510, BF131863, AI671536, BF242851, AI870629, AW514766, AI813311, AI862663, BE293244, AI768533, AI823596, AA129467, AI446582, AI435116, AI627345, AA972422, AI968606, AI088367, AI827354, BF439637, AI824877, BE220123, AV703921, AW236583, AI377591, AI040592, AA648774, AI095815, AW953613, D59730, D59523, AA029160, AW009152, AA054405, AI244209, AW023899, BE674038, BF059180, D59622, AA778356, AI470145, BF378975, AA970493, AI368877, D59801, AA129466, AI659586, AI344665, AI824866, AI803930, D59455, AA993837, D59633, R61441, AA704531, AW022576, AA484947, BF955158, D59447, AV725111, BE870487, AI082578, R35366, T74319, BF948389, D59583, D59781, R35909, AI365131, D59454, AW341984, BE467192, AI864239, D59649, D59777, H09254, T89104, AI128531, H23419, D59584, H09679, R23394, T77005, D59540, F13041, F10282, D80153, D80213, F10633, D59650, AA333625, BF855208, D59537, D59800, D59536, AI867775, AI702258, D80146, D59825, D59539, R25274, AA301260, D59438, H23420, D80341, D59769, D80323, AA827217, D59439, D59794, D59473, AA319561, R38088, R44178, R20566, D59692, F16283, D80260, R61396, D59749, AV726311, AA095729, D59772, AI088314, BF967226, AI383053, D59813, H22900, R14241, D59752, R40536, T34343, BF510049, F13475, D59782, AA346675, D80245, AI434889, Z43638, D59459, AW303981, D80381, BG054921, AW291373, D59812, AI418992, BF948033, AW516233, AI434666, BF837006, AW816352, AI356833, BF771676, AW340432, AA331587, AA332355, BF156021, AF353992.1, AK026257.1, BC008873.1, BC006150.1, AL512689. 1.
HMEFT54	113	520307	1 - 582	15 - 596	AI925461, AI187417, AA527170, W51933, AA534506, AI699870, AA430389, AW264729, AA284284, D20078, AI350867, AW131222, W48637, AA400891, AI458334, AI168826, AA400960, BF590627, AV719049, AV699669, AI557751, AW962245, AW975618, AA365173, Z21582, C14298, C14331, C15076, AV699550, AV724520, AW973541, AV718692, AW950117, D80064, AV719758, AV718489, AW949498, D59787, D59467, AA526218, AA701131, F13647, AW817409, AA434346, D80164, AV729929, AW964468, AI201668, D59889, D80195, AA507526, AV720791, AV718530, AI694178, D81030, BF382730, AV720203, AW960553, D50995, AV700889, BE148028, AU119190, R20046, BE001177, AW949645, D80196, BE748599, D51423, T41134, BF837744, AV718800, BF876179, D80212, C14227, BC002933.1, AK026989.1, AF254260.1, AL136917.1, BC008301.1, AF086205.1, AF254860.1, AC090939.1, AC005230.1, AF037338.1, AC004823.1, AC004922.2, AC020716.3, Z95116.1, AC025166.7, AL445184.11, AC009131.6, AC006581.16, AC010530.7, AP000172.1, AC003101.1, AP000057.1, AC005038.5, AP000125.1, BC005232.1, AC002407.1, AL031985.10, AC007308.13, AC002492.1, AC007021.3, AC012476.8, AP000688.1, Z98884.11, AC006241.1, AL355312.24,

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HMEGF92	114	520304	1 - 615	15 - 629	T65556, BF952979, F09666, AA995112, AA983746, AA983748, AP001972. 4.
HMSDL37	115	973996	1 - 2483	15 - 2497	BF358189, BF358186, BF358188, BF673854, AV762975, AA481760, AL042906, BE908602, AU154050, AU158859, AI310464, AA113159, AV718718, AW080062, AI952885, AL042905, BG029899, AA679794, BF813805, BE206133, AL048969, AI132963, AW401509, AV700988, AA113272, N49425, BF968610, AW975169, AA524604, AW157616, BE300645, AW008089, AV699423, AW976010, AV700654, BF679169, AI016704, N80210, AW151713, AU117926, AA427470, AW957502, AV760701, AI631119, N48230, BE895796, AW962035, AW979158, BF673743, AL534685, AA833875, AA833896, BF926318, BE061906, AA081138, AL044339, AW268329, AW960015, BG254652, AW600804, AU140392, BF820678, BF668559, AV764259, AA572968, BF736198, AV734543, BG222875, AW897556, BF892846, AC022001.3, AC018811.4, AC018494.6, AL353810.9, AC005553.1, AL139396.17, AL020995.14, AL163151.1, AL021918.1, AC022534.7, AL135903.12, AL161443.13, AC007912.6, AC018684.3, AC019052.7, AL163248.2, AJ400877.1, AC006313.1, AC022401.3, AC025165.27, AF274857.1, AL445186.4, AL137782.9, AL139322.13, AL355520.8, AC003065.1, AC004813.2, AE000659.1, AL139109.14, AC027670.4, AC021396.6, AC005033.1, AC007251.3, AC015723.8, AL392106.4, AC004073.1, AC007963.7, AC006544.19, AL353788.33, AL133500.3, AL512641.9, AC010376.5, AC073964.3, AC004650.1, AL157955.5, AL358372.11, AL359077.10, AL137918.4, AL035608.11, AL138783.6, AL135924.11, AP001189.4, AP002453.3, AL133373.5, AL391122.9, AL023876.2, AL163209.2, AC021093.16, AP001719.1, AC068643.27, AL121755.23, AC007068.17, AL359332.2, AL133241.3, AC007611.5, AL357060.31, AC078841.4, AL138880.14, AL159140.4, AL513264.8, AL138920.11, AC004021.1, Z92547.1, AC068102.4, AC089987.26, AC009289.8, AL163280.2, AC010282.5, AL157827.17, AJ006997.1, AC005066.1, AL163303.2, AC009122.8, AL035090.10, AL359205.15, AL133417.10, AC090497.2, AC007097.4, AC005280.3, AL359400.4, AC010591.8, AL354868.10, AP001718.1, AF131216.1, AC068312.4, AL109865.36, Z84480.1, AC009404.5, AC006543.7, AC007510.6, AL160162.11, AL354942.10, AC005862.1, AL136090.12, AC084882.2, AL353812.13, AC022740.4, AC008863.7, AC018797.4, AC006348.3, AL359644.10, AC008701.5, AC087427.2, AC074391.5, AL035407.15, AC010292.7, AL512310.3, AC020717.3, AC010885.8, AF235098.1, AL161629.10, AL035468.3, AC007447.6, AC007455.7, AC007385.3, AL390121.6,

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HMSFI26	116	560229	1 - 1203	15 - 1217	BF902399, W89152, BE391139, AW975663, AA767864, AW020255, AW021440, AI024622, AA730474, AA551532, AC069548.4, AC004906.3, AC004675.1, AC006965.3, AF088219.1, AL121574.19, AL139109.14, AC004813.2, AL162231.20, AC013734.4, AC012459.7, AL157955.5, AL391827.18, AC022407.6, AL034422.24, AC004216.1, AC011551.3, AL355336.15, Z83822.1, AC010252.3, AC008720.6, AL391122.9, AC000353.27, AC012377.5, AC011816.17, AC004408.1, AC007363.3, AC073101.7, AC010092.4, AC016396.5, AL117355.5, AC022201.4, AF235098.1, AL157372.18, AC007228.1, AL445237.16, AC008066.4, AL591770.1, AL162831.5, AP000355.1, AC026770.6, AL353588.25, AC006461.2, AC005840.2, AC005912.1, AC011456.2, AC009137.6, AL035079.14, AB042297.1, AL365400.19, AC003950.1, AC027126.4, Z98884.11, AL034369.1, AL031670.6, AC090955.2, AL157893.16, AC004685.1, AL133500.3, AC011497.6, AC018500.3, AL158206.8, AC019171.4, AC025168.7, AL034346.31, AC005736.1, AL133279.7, AL391724.7, AC002565.1, AP000284.1, AL080315.18, AL133410. 31.
HMVBS81	117	639203	1 - 515	15 - 529	AW080812, AW082817, AI951822, AW328562, BE138773, AI453744, AW246456, AW248692, AI953814, AA916922, AW166193, BE741575, AI189652, AI554578, BE207752, AW051430, AI143755, AW631158, AI378866, AA602780, AW166148, AI346750, AA402608, AI191618, AA643353, BE207747, AA703840, BF969135, AA503856, AI991172, AI150232, AI885695, BE312018, AA599791, BF940193, AI951334, AI192449, AI423588, AI089026, AI564055, AI160783, BE904552, BE675401, AA722619, AI333580, BE465600, AI147788, AI201929, N39330, AI806345, AA740539, AI359694, BF569026, BG111020, AW078736, W42999, AA915948, BG231541, AI453740, AA845228, AA128902, AI262427,

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HMWDC28	118	460487	1 - 1132	15 - 1146	BF511110, BF511098, BF507863, W52839, AW194969, AI199267, R68505, AI521938, R46033, W81166, BE000169, N47371, BE814496, W81165, AA086195, T64991, AI827849, AI816972, BF592053, AI797732.
HMWFT65	119	562063	1 - 1332	15 - 1346	AW795416, AL121287, AL133445.4, Z85996.1, AL034548.25, Z98304.1, AC004953.1, AC068799.14, AC074121.16, AC004905.1, AL031431.8, AC003982.1, AC006487.8, AC005971.5, AL050335.32, AL009181.1, AC010271.6, AC006483. 3.
HNEEE24	120	553558	1 - 1065	15 - 1079	BE695767, H18634, R44271, AA022988, AA454219, AA454220, AA022950, AA429414, BF112103, AI183463, AW293235, AA584870, AI608821, AA564655, AI467968, H69890, Z95152.1, Z77249.1, AC004837.1, AL050335.32, AC009399.5, AF222686.1, AD000090.1, AC069539.4, AL139080.11, AL117338.15, AC005000.2, AP000427.3, AF039905.1, AC027319.5, AC004996.1, AC010328.4, AP000043.1, AP000111.1, AP001716.1, AP000424.3, AP000292.1, AC073321.4, AL133330.14, AL138743.5, AL050338.12, AL445423.13, AC068715.5, AC009003.7, AL450026.10, AC008493.4, AL355334.26, AC002300. 1.
HNFFC43	121	753337	1 - 2089	15 - 2103	AL048903, AI678076, BF527660, BE728354, BF317174, BE409263, AL530934, AL042801, BE729268, AL041340, AL530935, BE314879, AL042802, AW190561, BE313085, AI961484, AU154235, AU132769, AW027201, AI424792, AL524550, AA864499, AI432437, AA917094, AI934618, BE327057, BE383358, AI499074, AI344032, AI955647, BG253760, AA572961, AL048902, AW769938, BF509684, BE208853, AI342638, AI761488, AW732625, BE259667, AW974120, AI564533, W51904, AW961340, AI289643, AW971194, AW272378, BE297579, AI867205, AI796156, AA884306, BF002574, BF927739, BE885728, BF847648, AA456581, AA918441, AL524551, BF918942, AI766564, AW769937, AA493778, BF918936, AA304712, BF869582, AI168435, AU126961, AA298993, AA377693, AW769673, AI383037, H67555, AA322347, AA221032, AA713594, AI366484, AL039675, BE273248, F24965, AW797208, AA426295, AA322180, AA322590, BF919436, BF919454, BF919453, BF919451, AW178871, AI538564, BF752997, AI766348, AI701097, AW080090, AI367680, BF812961, AI619820, AI633125, AI828682, AI818240, AW152182, BF811804, AI796113, BF968679, BF669151, AI800648, AI500714, AI702073, AI884318,

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					AK026746.1, AL110158.1, AF184965.1, X78627.1, AB047627.1, AL133623.1, BC009294.1, AY034001.1, AK026532.1, AL162002.1, AF026816.2, BC000199.1, BC008649.1, BC003591.1, AJ299431.1, Y13350.1, AK025099.1, BC004362.1, BC007460.1, AL512733.1, AB056420.1, BC008075.1, BC000090.1, AK025798.1, AF106697.1, AL136889.1, AL136893.1, AF199509.1, AF124728.1, U37359.1, AK025113.1, BC008078.1, BC004556.1, AF202636.1, D44497.1, AL133049.1, AF061573.2, AL157433.1, AL136784.1, BC008417.1, BC005070.1, AK026528.1, AL137478.1, X83544.1, AB060834.1, AL136844.1, AK000266.1, AL357195.1, AK027160.1, BC001305.1, AL137488.1, AL117435.1, X99226.1, BC004222.1, AL137550.1, AL161628.9, BC007021.1, Y14040.1, AF218000.1, AF141289.1, AK026613.1, AL117460.1, AF126488.1, AL080139.1, AK027365.1, AJ296345.1, AL137298.1, AL137716.1, Z35309.1, AL137627.1, AK000476.1, AK026550.1, AL359624.1, AL389939.1, AB048953.1, AL512684.1, BC000253.1, BC002370.1, BC002849.1, AF217987. 1.
HNFIY77	122	634551	1 - 1198	15 - 1212	BE778688, AA350580, AW451334, BE247283, BE242191, AI640492, AA078462, BE242141, AW003105, AA336368, R54889, AI910199, AI871293, AI267818, BF204188, AI858691, AC009412.6, AC072052.6, AL033517.1, AL161747.5, AC018897.4, AC005663.2, AL139095.15, AL135744.4, AC008072.3, AC005484.2, AL121897.32, AP000359.1, AC079141.7, AC020955. 6.
HNFJF07	123	577013	1 - 602	15 - 616	AA487061, AA486615, D78759, AC002091.1, AC004089.25, AC005015.2, AC039056.7, AC006329.5, AC005081.3, AC084693.2, U91323.1, AC002352.1, U82668.1, AL391259.15, AL109897. 30.
HNGFR31	124	553552	1 - 522	15 - 536	AL360297.12, AC005023.1, AC022124.5, AC008390.7, AC004836.2, AL136984.20, AC009558.14, AL117373.14, AP002350.3, AC006265.1, AC007057.3, AL139233.8, AC005079.6, AL359824.17, AP001541.4, AP000426.3, AJ239322. 3.
HNGIJ31	125	519120	1 - 782	15 - 796	AU147901, AA376128, BE562634, AC051619.7, AC020629.6, AL445531.10, AC009412.6, AC005052.2, AC079383.17, AL009172.1, AC016637.6, AK022380.1, AC004032.7, AP000555.1, AC009789.21, Z83851.17, AL359643.27, AC011005.7, AC008521.5, AC008635. 6.
HNGJE50	126	561568	1 - 1023	15 - 1037	
HNGND37	127	839224	1 - 827	15 - 841	AA774312, BE670568, AI298480, BE702731, AI088824, AI149772, AA976633, AI870274, AA010606, AA010607, AW957725, AA010628, T33898, T75431, AI355909, AC005300.10, AC006946.20, AF307451. 1.
HNGOI12	128	104137 5	1 - 2114	15 - 2128	AJ006345.1, AC005950.1, AC003675.1, AC001228. 1.
HNHEU93	129	634851	1 - 734	15 - 748	AW502688, AW410844, AI444575, AW504667, AW157128, AV758849, AW974923, AI038029, AA533011, AW021674, AW731858, AA618531, AA554289, AA557945, AA046906, AI065031, AW963552, AL121039, BG180320, AI702049, BG059139, AA157876, BE080768, AI567676, AI745666, AV732057, AW953437, N72678, H53546, AL044966, BF942991, BF679568, BF724416, AI003068, BG059924, AA640305, BF439153, H47461, AA507623, AI921744, AA935827, AW265468, BF589864, AA831714, AW020682, AI572680, AA601336, AI791720, AI791408, BE049409, AI114755, AW962971, AI828721, AU158433, BE244547, AI251024, AV730440, AW148821, AW474825, AA631915, AI791659, AA595661, AA610644, AW023975, AA657392, AW029626, AA834891, AI884404, AV743067,

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HNHFM14	130	664507	1 - 283	15 - 297	AC020552.4.
HNHNB29	131	895462	1 - 1880	15 - 1894	AI049955, AA904211, AI921765, AU146342, R98218, BF725178, BF337320, AA515728, AL524675, BF772474, BG057207, BE675681, BE063437, BF804385, AI962030, R74433, BF724699, AV656063, AI499954, AI653776, AI523074, AI362442, AU118374, AW023302, AW957372, BE150793, AV763026, AV763058, BE281645, AW410354, AL038842, AW963444, AW403829, AA503298, AI709307, AW023111, AA825827, AV756491, AU158454, BF877926, AA713705, BG236484, AI735609, AW082104, AW780190, AV760014, AI254779, AA558404, AV719392, AA502532, AI114704, AA833875, AA833896, AA832145, AW957600, AA644090, BE072475, AW575605, AV703785, AW503420, AW973992, AI802087, BE301610, AW302017, AV738383, AW237905, AI859438, BF760573, AW962611, AV733437, BF944736, AV647070, AW513789, BG110818, AA581247, AI687343, BF854308, AW970958, AW615560, AI755057, AU157093, AI821987, BG222875, AA714110, AI732869, AA811741, AW849714, AL079734, AI889995, AA452887, AW978041, AV740009, AV764259, AA084609, H63660, AI587349, AW965008, AW190484, BE677244, AW501542, AW236219, BF217723, AA056248, AW843204, AV695478, AA633875, AW978591, AW192373, AW957154, AA604831, AW303872, AI141130, BF977305, AA297776, AI160786, AU151428, AU150634, AW083934, AA613624, AW051819, AI961983, BE968477, AW510513, AI417469, AC084881.19, Y10196.1, AL357515.26, AC005736.1, AL139396.17, AL356415.26, AC006241.1, AC006121.1, AL590763.1, AL022316.2, AL096677.21, AC016597.4, AF053356.1, AC002996.1, AL158040.13, AC012320.6, AC013434.8, AL109843.25, AC009194.8, AL356020.3, AC002425.1, AL133448.4, AC020916.7, AC005081.3, AL161731.20, AC078846.2, Z83819.1, AC011247.10, AL139317.5, AL022323.7, U95090.1, AC007225.2, AC083884.6, D86995.1, AC020913.6, AL356915.19, AL050349.27, AC023425.20, AC034242.5, AP001705.1, AC008946.6, Z95331.2, AP002008.5, Z98752.16, AC005920.1, AL157838.24, AL135839.15, Z93023.1, AC002045.1, AC005522.2, AC010419.5, AC016655.6, AC008616.6, AP001718.1, AL161669.5, AL035684.25, AP001752.1, AC002369.1, U95739.1, AC026794.4, AC015982.9, AL121586.31, AC009087.4, AC026202.6, AC008733.7, AL133477.16, AC005015.2, AL023575.1, AC007685.2, AC008397.7, AC018644.6, AL137061.12, AP001922.4, AC011442.5, AC006430.22, AC008766.4, AL132639.4, AC018821.4, AC006334.3, AC002492.1, AL157372.18, AC002073.1, AP000501.1, AC011465.4, AC022404.7, AC018639.8, AL135783.6, AL358434.16, AL031295.1, AL353807.18, AL157791.4, Z99716.4, Z83844.5, AP001709.1, AL031311.1, AC006040.3, AC067941.7, AC009032.7, AC007404.4, AL022326.1, AC018523.9, AC008755.6, AC008622.5, AC009996.7, AC008403.6, AC000353.27, AP001728.1, AP002007.4, AP000152.1, AC011287.4, AL021026.1, AC090950.1, AL049643.12, AL392106.4, AP001711.1, AC006028.3, AC008745.6, Z83822.1, AL136040.5, AC025280.4, AC010150.3, AB001523.1, AL159191.4, AC078957.16, AC020906.6, AL096701.14, AL138920.11, AC010271.6, AC022116.5, AL162426.20, AC004685.1, AC025159.28, AL139353.3, AF139813.1, AC007462.2, AC008904.6, AC013355.7, AL390241.19, AC022217.5, AC009165.6, AC004491.1, AP001670.1, AC007546.5, AL121899.37,

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HNHOD46	132	843488	1 - 1341	15 - 1355	AV700498, BG164166, AV700988, AV700545, AL037632, AV762783, BG260565, AV714931, AV760723, AF074667, BF792326, AF034176, BE796439, AW962035, AW976010, AA524604, AV760360, BE541237, AU118837, AV719941, BF678427, AL138265, AW188427, AV733710, AL048626, AU117926, BE909125, AV764490, AU119532, BE067011, AL534817, AV699709, AV686853, AV722030, BE393367, BE538259, AA708751, AI732911, BF346320, AW970915, AA526787, AW131249, AU147226, AV763174, AV760497, BF805173, BF968141, AV762900, AV759711, AV759356, AV760364, BF307044, AV762902, BF679169, AV759686, AV762779, AW963982, AL042906, AV759684, AV762001, AV759683, AL135377, AV734543, AW408643, AU155227, AV759046, AA601355, BF913258, BE273856, AL044340, AA081138, AI952885, AA584482, AV734401, AL042905, AV722075, AV737621, BF666736, AA211734, AW080062, AV762002, AV761309, AI791227, AW961160, AV763305, AI038990, AV759172, AW102955, AA708108, BF381650, BF828714, AI685198, AI679294, BE066950, AV763952, AA831913, AI679871, AU145521, AI204309, AW151713, AW069670, AA481760, BF892846, AW130036, AV763135, AU140392, AA284247, AW102811, AA722372, AW008212, AU158859, AA640277, U51704, AU155168, BG258140, AW088689, AU155048, AA577824, BE387734, BE867712, AL119123, AW079809, AA601326, BF968610, AA515829, AC008440.8, AC011531.7, AC002302.1, AC027319.5, AC005484.2, AC005972.1, AC010469.7, AL109743.4, AC005077.5, AL035398.19, AC020916.7, AC022211.5, AC002301.1, AC018808.4, AP001711.1, AC008745.6, AC000052.16, AL035587.5, AC008720.6, AC007421.12, AC003101.1, AC034193.4, AC025593.5, AC006511.5, AF045555.1, AC007374.6, AL096814.26, AC005081.3, AL445685.17, AJ400877.1, AC004985.2, AC020558.4, AC009516.19, AC008443.8, AL031447.4, AC006028.3, AL121992.24, AC011465.4, AC008655.6, AC008616.6, AL135928.6, AL513550.9, AL031295.1, AL050335.32, AL049780.4, AC005052.2, AL390060.14, AC011005.7, AP001717.1,

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HNTBI26	133	131082 1	1 - 1368	15 - 1382	AL528533, AL520935, AL521290, AL515806, AL520965, BE293492, AL520936, AL515807, AW972854, AV753139, BG178370, BF968317, AL520966, BE780476, BE305183, AI678037, AW293248, AL521291, AI269883, BF978348, AA894746, AI493776, AA778869, AI424848, AA525497, BF307374, AA622403, BG109953, N21347, AI095265, BF792489, AL519236, AA564674, BE249905, AI268502, AA995849, AA894745, AI249680, AW087844, AI300762, N72839, AI244187, AI089147, AI368934, AI740804, AI339842, AW516709, BF315359, AI335796, AW192649, AW801578, N28008, AI095231, BF977145, BF977663, BF765528, BE778762, BE875935, AI951011, BF669511, BG033337, AW393151, AL519237, AW819092, AW393138, BE868896, AV691113, BE875559, AV693124, BF976999, BF690855, AI127890,

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HNTBL27	134	545534	1 - 777	15 - 791	AW169270, BF475369, AL524823, BE903984, AL530691, BE536833, BG230736, BE881512, BF033804, AA716162, AW183635, AI188277, AI141766, AI624087, AW173452, AI129419, AI683124, BE903838, AI828817, AI308087, BE544869, BF061917, AW291854, BE880241, AW471490, AW615124, AA701470, BF447518, AW025680, BF094269, AW449210, AA315210, BG251005, AW504333, AI239598, BE697836, BE742666, AI284846, AI355748, BE899398, BG027544, BF352604, AW376334, AW376337, AW752527, AW194025, AI890712, AI565340, BC006846. 1.
HNTCE26	135	116039 5	1 - 2149	15 - 2163	BG252201, AV726464, AL529709, BE894106, AV726994, BF970560, BF132059, BF977798, AI703275, AW512938, BG164577, AL529708, AI767521, AI823746, BE220262, AA583438, AI143608, AW468337, AI949854, AV727138, AI620344, AI209187, AI630993, BG007081, AI004986, AI565892, AV715169, AI367983, BF056815, AW394003, R70620, BG007658, AA152183, BF381743, AA565300, AA088574, AA931697, AA995899, AI025252, AA297479, T84083, AW138535, H71679, Z45535, AA297478,

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HNTNI01	136	135228 5	1 - 2073	15 - 2087	AA447485, AA196688, M86015, AI750365, R13985, BF356780, N28763, AC005028. 1.
HODDF13	137	684307	1 - 816	15 - 830	AC011245.8.
HODDN92	138	422913	1 - 1925	15 - 1939	BG116781, BG110501, BE150456, AI742087, AA453725, AI917507, AW769479, AI860142, BE326465, AI459289, AI860141, AW963123, BE646467, AA868553, AW872412, AW971193, AW277065, AI921333, BF576826, AI024689, BE466760, AI354470, AI005467, AW103830, BE045272, AI827987, AA442638, BF109829, AA813604, N28268, AA442648, AA563934, N63406, AA833517, AA663108, AA437299, AA632986, AA436880, N58885, AA812876, AA447794, AA442379, N58892, AW020895, AA522837, AA600372, AA229448, T78981, AA663178, AV693238, AI187977, AV696576, AI472712, AA229164, T85178, AW270324, AV683374, R64648, AA333708, AA703066, AW961515, BE093710, T78927, R64655, BF802058, R95914, T84294, AA551512, AA460220, AI916737, R31132, AA359583, AI217018, N56349, AI191725, BE835233, BE835385, T84796, AV741009, BE835410, AI084517, N83238, AW362842, AA247541, R31089, T91125, AA493776, BE818350, BE818352, AI253986, R31247, AW303285, N95696, BE708493, AA678297, AI003856, BE818343, N95562, AW024721, AA862707, N95587, AA401399, AA399957, AW511080, AL157879.7, AL021368.1, AL009030.15, AL049987.1, AL133255.13, AL390738. 4.
HOFMQ33	139	118446 5	1 - 2396	15 - 2410	AL528504, AU121718, AI820674, T94707, AJ224741.1, Y13341.1, AC079145.3, AJ001047. 1.
HOFOC73	140	931871	1 - 1477	15 - 1491	BF195687, AI762843, BF435173, AW167715, BE675436, AI829951, BF195590, AW517368, AI831464, BF110813, BF939079, AW573230, BE747230, AI760936, BF348602, AA418800, AI870845, AI420441, AI377190, BF196297, N32270, AI813507, AI313119, AI472198, AI340272, AA502942, AI363372, AI806717, AI479956, AA861188, AI073435, AI128897, AI799480, N35138, AA832426, AW753935, AA421515, AW362239, AA258517, AI907351, AA789084, BF924856, H42825, F35882, BF814541, AW409775, AW265004, AA830821, AW089179, AL133741, AA835966, BG029053, BE781369, AI696969, AI565172, AW089006, BE965169, BF527012, AA807088, BE048071, AI567637, AW088899, AI571868, BF725863, BF970263, AI244380, AL119791, BG058039, AW020419, BE964497, AW999906, BE785868, AI400725, AL046463, AI874166, AI922577, AI874151, AW081034, AI620093, AI282903, AI280661, AW193203, AA603709, AI570966, BG260144, BE061389, AI537617, AI919345, BG027628, AW130863, BF915537, AW834355, BF815196, AI648567, BE963918, BF915208, BE072233, AI952302, AI805638, AI366549, AI636719, AI539153, BE964767, AW085786, BE538466, BF904180, BE172499, BE963286, AL036638, AI857760, AA568405, AI611743, AI689420, AW083804, AI696626, AI633477, AV757067, AI589993, AI365256, T99953, BG105895, AL038505, BF814449, AW022682, BE393551,

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HOQBJ82	141	135235 6	1 - 3516	15 - 3530	BE904978, BE383830, BE890564, BE729647, BE732309, BE789481, BE886173, BE733387, BE386405, BG258301, BE383286, BF125887, BE777790, BE280391, BE515074, AI459129, BE281548, BE644930,

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HOSBY40	142	589431	1 - 1131	15 - 1145	BE465874, BE465890, AW418562, AW814995, AA721114, AC002543. 1.
HOSDJ25	143	854234	1 - 2200	15 - 2214	AL521533, BF966564, BG109192, BE621548, BG259805, BF666690, BF667661, BF185318, BF666019, BE621125, AI433432, AW963800, BE883279, BF028488, BF667980, BF196902, BF111775, BF667265, BF664922, BF966437, BF667218, AI277896, BF028500, AI401346, BF696865, BF698781, BG169528, BF696312, AW338135, AI280253, AA873621, AI435513, BE552077, BF699387, BF055949, BF697521, BE542555, AI277959, AA121788, AI961880, AW969937, BF478121, AW338124, AA528626, AW367010, R76478, AA101422, T62844, AI918990, BE167397, W72961, AA876737, R28131, BE176581, AA375127, BF332407, AI365181, W73131, T62693, W21429, N92911, BF570557, AI077290, AA127501, R66340, AI926197, C00153, AA813575, R28517, AI580500, AI222072, AI033269, AA758476, W86851, AV661704, AV725920, AV728997, AV704234, AV726624, AV655280, AV729378, AV708992, AV727787, AV709407, AV654908, AV660608, AV652001, AV656903, AV707541, AV706854, AV702117, AV726738, AV728733, AV708834, AV687035, AV697196, AV708704, AV659322, AV656478, AV698545, AV709314, AV708381, AV660728, AV691080, AV651955, AV703169, AV728518, AW952409, AV709660, AV729220, AV696866, AV726816, AV695545, AV656283, AV708025, AV707933, AV684604, AV708980, AV692691, AV701914, AV705159, AV702516, AV693523, AV726103, AV727029, AV725826, AV725134, AV705280, AV702994, AV683272, AV697288, AV652156, AV728670, AV708723, AV729263, AV707510, AV699089, AV658863, AV701560, AV727776, AV698609, AV696106, AV706744, AV708438, AW951263, AV689111, AV728157, AV708109, AV692345, AV704553, AV683443, AV708893, AV659536, AV706219, AV658275, AV705693, AW960720, AV686064, AV705632, AV706721, AV701067, AV709604, AV704955, AV701707, AV707753, AV706089, AV704269, AV703495, AV702021, AV706677, AW960326, AV709869, AV656256, AV687909, AW954031, AV702832, AV708622, AV729259, AV726784, AV702833, AV707296, AV707767, AW958647, AV654896, AV645906, AV728806, AV652617, AV703599, AV727990, AV701580, AV708004, AV727003, AV703970, AV727526, AV727799, AV728471, AV703472, AV702147, AV686060, AV726156, AV649758,

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HPIBO15	145	131086 8	1 - 1725	15 - 1739	AI056404, AI802391, AW270724, AI750249, N41425, N47678, AI188511, AI376981, AA029314, AW452123, BE466507, N39755, AI937190, AA063620, AA693737, AI139466, AA701241, AI250789, AI672263, AI198257, BF055537, AI199035, AA677064, W69895, AA040154, BF196981, W73711, AA029867, W69841, BF222273, AW900121, AW022270, W69574, AI373227, AI200161, AA701858, AV690112, AW044223, W69662, AI052153, AA872860, H29417, H29324, N26312, AI283749, AA036704, AI383659, AA332627, N47677, AI424682, BE089934, AA329748, AW952484.
HPJBI33	146	685699	1 - 1663	15 - 1677	AI679782, BE796439, AV763892, BE387734, AW303196, AW301350, AW274349, AL046409, AI204304, AU148742, AL048142, F36273, BF475381, BE156019, AL041690, BE872393, N94311, BG236735, AA599480, AW630298, AW473163, AI754955, BF683672, AI281881, AW276827, AI341548, BF806176, AW467362, BF805094, BF940837, AV762050, BE350475, AA631507, AV652936, AW963497, BF965007, AV681599, BE042649, AV762139, AW080939, AW276435, AI291268, AI291124, AW339568, AU154961, AA426277, AI133164, AW088616, AI951863, AW873530, BF816072, AL038785, AW148792, AW338086, BE869857, AW408717, BE042475, AI580652, AA525190, AL044940, AV760466, AV713243, AW969694, AI537955, AC005527.3, AL050318.13, AC010279.4, AC000025.2, AF134726.1, AC008736.6, AC004983.2, AC004965.2, AL162458.10, AC009269.6, AC020552.4, U91321.1, AL136179.15, AC011455.6, AC020916.7, AC084783.2, AC009244.24, AL133332.12, AC009144.5, AC005755.1, AC013449.8, U95740.1, AC010319.7, AP001725.1, AC008068.4, AC011497.6, AL021546.1, AL121586.31, AC004971.3, AL021391.2, AC007055.3, AC011464.5, AC010422.7, AC006430.22, AL390738.4, AL109805.14, AC006483.3, AL033528.19, AP001716.1, AF053356.1, AP000112.1, AL160271.19, AL157882.5, AL022323.7, AC018751.30, AL121900.26, AL356354.10, AL121897.32, AC006435.7, AL160471.5, AC027689.10, AC004878.2, AL121903.13, AL121890.34, AP000044.1, AP000513.1, AC004662.1, AC027319.5, AC011236.8, AC008738.6, AL136980.5, AC020904.6, AL132640.4, AC009516.19, AC018506.4, AJ400877.1, AC003003.1, AC016587.7, AC004847.3, AC012476.8, AP000555.1, AC020931.5, AC018719.4,

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HPMDK28	148	846357	1 - 1070	15 - 1084	BG112660, BG025264, AL528310, BG168817, BE744551, BE877617, AI356771, BG163540, AA203523, BG031683, BF822950, AW592567, AA176981, AA904437, BF209639, BF312400, AU134583, BF194783, BF058517, BF445932, BF115227, BF732680, BF445936, AW303381, AW149649, AW027536, AW583459, AW475091, AA065227, BF869433, AW103970, AA703536, AA902103, AI735312, AI082224, BE262098, AW405660, AW009422, AA932869, BF940753, AI830877, AI830074, BG222176, AI742006, AI381584, AA133474, AI347025, BF869417, AI452483, AA993536, AW954279, BE737248, N66683, BE261151, AI369439, AI334008, AI005081, AL528309, BE166345, AA365303, BF222033, F32952, AI697441, AA488152, AI418548, BG248769, AI279351, AI888277, BF115544, AI200343, AA977299, AI612818, BE163359, AI830668, BE740423, AW574601, AA315546, BE397815, AA573402, BE004351, AA573411, AA633508, BF925742, AA741489, H82686, BF894571, AA065233, AA360707,

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HPRAL78	149	135234 2	1 - 2058	15 - 2072	BF342508, BE745079, BF316647, AW954022, BF219864, BF220093, BF182978, BG108443, BE879671, AI684112, BE840525, AW957217, BE840530, AI148569, AI128199, AL041807, BF027688, AA401860, BF915566, BF914452, AA938143, AA588312, AI991034, AI672251, AI862148, AI333529, AI798586, AI095534, BF826436, AA976203, AA424398, AI475525, AL039685, T52017, AI055912, R51437, AW071787, AI598282, AA578538, AA554343, AI140222, AW268634, AI300146, AA340540, AA411182, C04045, AI926947, AW088744, AA757547, AI798454, AW473352, AV691484, AI076726, AV647523, AW475065, AA364829, AW028194, AW249610, W22554, H66782, AA081290, N95459, W25198, R60726, AI311111, AI351724, AW614976, AA506965, AI142999, BF091172, AA604134, T63960, BE840632, AI583100, AI351726, AW009121, AA081115, AA081697, AA411256, BF679941, R60727, AA578520, AW129067, AA612772, AI824391, AA470674, H66783, AW953852, AW006565, N34727, AW160746, AA832062, R36715, R90863, R84524, BF924179, H12158, AW770335, AA315553, AA702770, AW246146, AA370468, AA832305, AW082570, AI568825, BF929006, AA251006, AA043375, AA508725, AW068182, AA766464, BF769780, AW316684, BE260322, BE819573, AA082047, AA370467, BF929011, BG056952, AW241232, BF751574, AI686507, AL050275.1, BC008720.1, AC022007.3, AC018809. 4.
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HRACD15	151	871221	1 - 1525	15 - 1539	AL519765, AL519766, BE910445, BF684654, BE270497, BE513843, BF975936, BE396890, BF973472,

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HRACJ35	152	877666	1 - 2063	15 - 2077	BE906771, BE218907, AI912661, BE670671, BG166321, AW167740, AI698131, AI796048, BF476110, AW952474, AW474992, AW149683, AI814137, BF436724, AA452391, AI635719, AI422285, AI675301, AW301634, AI800309, AI023300, AI269915, AA054467, BF062213, AI220479, AA991181, AI159765, W88683, AI623293, AI205308, AA043330, AA461136, BE669608, AI032982, AA634903, AI361429, AA877688, BF681677, AW868366, AI683625, AI094869, AI268543, AI040482, AA460833, AI042583, AI800329, H40189, AA041196, AI420048, AA127006, AI023081, AA045134, T96696, M79132, W23483, BF000996, AI161385, BF476853, AI521085, AI984382, AA492294, AA016124, N95081, R13864,

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HRGBL78	153	910133	1 - 2094	15 - 2108	BE271199, AW575245, BF794609, BF797900, BE559773, BE384088, BE513826, BE270971, BF572042, BE560978, BF690655, BE674800, BE275832, BF303959, AW205367, AW402801, BF203242, AW402242, AW402928, BF305905, BE466652, BE892536, AW403946, N24246, AW968460, AI654541, N28316, BF572179, N29315, N38941, AW383418, AA458944, AI276242, BE729612, AA215300, N33010, AW383426, AW383396, N20230, BF692515, AI439520, N29316, AA459158, N25452, W03476, AW383428, AW402824, N30453, N28949, N21241, AI760983, N20533, AI434284, BG025865, N72999, N20563, BF896859, AW403434, N67502, AI470743, N73074, AA837208, AW407871, H84381, AW404443, N26470, W02963, AI864746, N46511, W02298, H98912, H84382, N35519, H99497, BF890914, AA761778, N71796, AI222330, BC006521.1, AL359541. 11.
HROAJ39	154	118169 9	1 - 1132	15 - 1146	T66247, BE081925, R34513, F12057, AA852760, AA125904, BF996914, BF107281, BF743278, BF742834, AB040901. 1.
HROBD68	155	827306	1 - 1984	15 - 1998	AI921101, AW102963, C17730, AW139132, AI499286, AU157470, AW157413, AW517766, AI285660, AL038713, AU146974, AA779937, AW272376, AI862212, AI246569, W58428, AU145383, AI051341, AI925647, AI869945, N77920, AI591332, AI440018, AU148220, AI872191, AV695638, T06365, AI310239, AI559442, AI818151, AA811111, AI453790, AA130476, F16040, AI685116, AI610326, BE646447, AA166854, AI540098, AI375417, AI887321, AA767353, AV693309, N20521, AI369914, AA846188, H96719, AA961590, AI088245, AA902828, BF112065, AA129986, AI439415, N30146, AI817158, N33132, N31608, AW084901, AA055654, BE245707, AI619818, AI628308, N20064, AV726924, AA347740, AA932087, AA657353, AA550798, AI028382, AW262471, AI147839, AA132716, AA460715, AI250812, H97388, BG027070, AW072619, BF002501, AI568919, Z36956, AI538654, N90055, AI376849, AI952804, AI264673, AA468571, AA584498, H04879, AA342051, AI733728, BF963854, AW962610, AA099788, AI858607, AI189033, AA157033, AI675848, AA722562, AA659014, AW468555, AA862135, AA911409, AA226507, AI244642, N24958, AW085676, AA169142, AA364962, AA569918, BF221900, AU156129, AV702748, AA016272, AI601265, AW272291, AI082077, AI376984, AI377100, AA864823, W16525, N26697, AL110383, AW088343, BE264670, T48029, T69889, AA724610, W96522, AA826143, AW753399, AI827133, AI783731, AI598077, AA565911, AL523955, BE677100, BF772474, AV695478, BF576607, AU143935, AL521095, H20876, W31567, BF805088,

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HSAWD74	156	460527	1 - 956	15 - 970	BG056446, N32720, AW152171, AA339555, AA076697, AA525291, AA380007, BE734992, AA077031, AA379882, BE047929, AA515728, AI282253, AA683069, AW275432, AW274078, AA533025, AI675615, AL040054, AA644090, AI345123, N42169, AW023111, AV756491, AI962030, AV758870, AW021774, AA602906, BG222564, BG222326, AV762454, AL048060, AA225406, AI879951, AA078830, AW514006, BE063437, BF725844, AI591299, AI590522, H68343, AA825827, AA559166, AW272294, BF213224, BE049095, AI344810, AA714011, AW502237, H63660, H24331, AA171400, AL449689, AI753113, F18888, AA282951, AV761486, AW193493, AA669238, AI557644, AI049868, AW631267, AA525331, AW117740, AA507623, AA862183, BE968744, BE677164, AW571963, AI433952, BF991881, AA701080, BF970107, BF212465, AA832175, AA470933, AW157128, AI343144, AW974751, AW338376, AW410409, AW844636, AW664505, AA827383, AV760014, AI745116, AI003611, AV683406, AW021154, AW501278, BE968477, BF991882, AI189682, AU124213, AI336637, AW572140, AA610644, AW963463, AA708322, AA489390, AI887235, AC004084.1, AC004951.5, AP000252.1, AP001711.1, AC006160.9, AP000031.1, AC022383.3, AC009131.6, AL354864.16, AL121900.26, AP000212.1, AP000134.1, AL031281.6, Z99716.4, AC009144.5, AC005015.2, AL137852.15, AP001207.3, AL035458.35, AP001753.1, AC026794.4, AL139022.4, AC009179.17, AL033383.26, AC090498.2, AC011472.7, AL162578.13, AL590762.1, AL117380.28, AF045555.1, AE006467.1, AC006088.1, AL096701.14, AL137881.12, AC011491.5, AC018828.3, AC005081.3, AC034193.4, AL110115.38, AB001523.1, AL023586.1, AL022237.1, AP000348.1, U91322.1, AL049591.12, AL133367.4, AC018808.4, AC091529.1, AC005666.1, AC011497.6, AL450339.5, AC004655.1, AP001718.1, AC005052.2, AC026866.8, AL136228.8, AC005793.1, AL139317.5, AL354720.14, AC004129.1, AL035461.11, AL161727.15, AF217413.1, AC007371.16, AL049539.21, AL008729.1, AC000353.27, AC003962.1, AC005940.3, AL158830.17, AF001549.1, AC004263.1, AC006441.13, AP000345.1, AC011811.42, AE006640.1, AL035086.12, AC004777.1, AC055120.5, AC002430.1, X02571.1, AC009477.4, AC006285.11, AC006597.2, AC018663.3, AC011479.6, AL139193.4, AC005692.1, AC009220.10, AC005907.1, AC007384.3, AC005049.2, AC004913.2, AC010328.4, AC005701.1, AC016025.12, U59962.1, AP003357.2, AC006345.4, AC006241.1, AL356805.5, AC004089.25, AC009247.12, AC005520.2, AC004910.1, AC027319.5, AC011495.6, AC008126.9, AC008521.5, AC005231.2, AC006449.19, AC002554.1, AL138720.19, AC011485.6, AL138875.8, AC008747.5, AC002994.2, AC003029.2, AC005291.1, AC006430.22, AL121712.27, AC078962.30, AL359082.16, AC004647.1, AC002429.1, AJ277546.2, AL133351.33, AL355102.5, AL391827.18, AL137140.12, AC004812.1, AC005098.2, AL390878.6, AL512883.5, AC090958.1, AC004883.2, AL135924.11, M12901.1, AL109984.14, AC018758.2, AL133477.16, AC012170.6, AC026185.3, AC005736.1, AC090426.1, AF283320.1, AC012499.7, AC011446.6, AC005288.1, AC005355.1, AC006581.16, AL162430.15, AL133500.3, AL109865.36, AC010271.6, AL445195.4, AC005005.1, AC003043.1, AL354815.10, AC083884.6, AC008755.6, AL021579.1, AL354935.23, Z81364.1, AL109925.11, AL139339.22, AC004876.2, AC020983.7, AF195658.1, AL022727.1, AC005598.6, Z93930.10, AC011480.3, AF312915.1, AC005220.1, AC074121.16, AL139123.14,

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HSDEK49	157	135225 3	1 - 1768	15 - 1782	AL513706, AL513705, AV700980, BF343961, AV710516, AV716397, AV715849, BF351156, AV717025, AW071975, AI922669, AI129815, BF106386, AA702864, W32947, AV690218, AV685715, AV693576, AV686846, AV695322, AV697709, BF924861, AI168499, AI343825, AA627735, AI554367, AI335089, AV697729, AI290781, AA875852, AA442570, AV686969, AV698914, AA486920, AI357884, AI088635, W79882, R39812, AV683817, BF932594, W17367, N78991, AA972857, R62969, R59135, AW961380, R56601, BE857524, R66262, W74268, AA436814, AA813538, H05057, AA133776, Z43556, R14044, R81029, T48889, AA228697, R56602, AA142932, R63023, Z39624, F02373, AA993978, R66723, R67603, R59136, R80928, AA133775, AW874480, T48888, AA228698, AA368546, BF525711, AA115592, AA328299, AA486747, BG001652, AJ132502.1, AL034397. 1.
HSDFJ26	158	834619	1 - 1191	15 - 1205	AI770009, BE467511, AW593206, AA434584, AI767843, AA780308, AA563708, AA317400, AA433906, AB021123.1, AC005598.6, AF361936. 1.
HSDSB09	159	130149 8	1 - 795	15 - 809	BF432333, AI861851, AI240993, AI795956, AI074484, AI640759, AW006868, AW241621, BF592070, AW271387, AW614840, AW450466, AW243423, AI244694, AI640517, BF431431, BF431530, AI439169, AI613108, AI915938, AI984796, AI245393, AW300335, AA931466, AW235983, AC005722. 1.
HSDSE75	160	545057	1 - 1137	15 - 1151	AW378251, BF349814, AA687791, BF739001, AW378183, AA661723, H61383, T88677, H62404, AA443169, AW339864, AA458622, AA252063, AI129690, AW960791, AB006755.1, AB006756.1, AB006757. 1.
HSIDJ81	161	589447	1 - 1289	15 - 1303	H27567, H27494, H71543, AI754653, BF857849, AW023111, AI521525, AW572721, AW963450, AI254770, AI926102, AV701462, AW020150, AI871973, AW500534, AW275432, AA218851, AA595661, BF854170, BF853574, BF853009, AW151247, AA536040, AW274078, AW958962, AI791659, AA669238, AI223626, AI249853, AW302048, BF725844, AI284543, BE139139, AW855625, AL042621, AW575000, AI801505, N68677, AI250552, AV758870, AW272294, H86725, AW851405, AI625604, AI251034, AA525807, AW075979, AI697235, AI090377, AA570255, AA702637, AV760014, AA729387, AA831426, AI697239, AI697242, AW504224, AI879951, AW502949, H77492, AW514065, AI224583, AV759203, BF527070, AA491767, AA229496, AL158830.17, AC005412.6, AL355855.23, AL132718.5, AL391868.15, AF285442.1, U91321.1, AP000505.1, AF129756.1, Y14768.1, AB000882.1, AL353804.22, AC005013.1, AC004448.2, AL139415.10, AC009309.4, AC091529.1, AL391122.9,

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HSKDA27	162	135240 9	1 - 4398	15 - 4412	BF338364, BG253437, BG122685, BF037455, AW303375, AW173315, BF037378, BG120262, BG117983, BF915045, BF057308, BG252401, BG034853, BF793365, AW379378, BF826037, AA570507, BF915582, BG122734, W07328, AA600736, AI971935, BE697573, BE313814, AI090486, AI751258, BE839359, BF447303, AW631492, AA625303, BF513067, AI609700, AI768270, AI751257, BE939504, AA417652, AI751036, BE378218, AI652363, AI971415, AA599207, AI371013, AA024968, AI147536,

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HSKGN81	163	676075	1 - 1893	15 - 1907	BG110811, BE745101, BE743722, BE545826, BE745120, BF681303, AW978606, AV702796, BE047756, BF848815, AW961578, AA446896, AI422823, BF848816, AI911304, AI038608, AA312710, AI143843, AI150244, BF829479, AI193547, AA705005, AI268239, AI140112, T65948, BE547522, AA393113, AI366477, AI085862, AI074853, AI277116, AI983894, AA394060, AA643650, AA100891, BF819277, AA922511, AV762171, AA478086, AI689302, AI275103, AI359079, AA532473, AV729423, BE349933, AI287604, AA477628, AV704180, BF847512, AI921910, AW105712, AW370596, AI624549, AW149890, AA505962, AA321215, AI357856, AA292337, BE292730, T34097, AW439882, AA447016, AI914726, R42595, AI858704, AI446219, AI275944, Z43230, BE707350, AW194214, AA135290, AW378090, BE241555, BE243232, AA010669, AW953547, AA632244, AW662488, BG057144, AW068278, R12726, BE151809, AW674205, T74373, N78860, BE242323, T31535, AI689506, R27706, F09665, R17501, AA435604, AW572245, BE548954, AI023355, BE545268, Z41318, AA383547, AA454729, AA570630, AA031630, AW173762, AW840945, AA381001, AA234325, T35951, Z45645, BE242712, T35949,

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HSNAD72	164	467397	1 - 847	15 - 861	AW971203, AW861646, AI610321, AI880774, AA829195, AI880765, AA551170, AI969833, AA133550, T61620, AV758870, AA557945, AW873417, AI635819, C06160, AV761107, BE268727, AA743968, AA845333, BF574331, BG222875, BF946125, BF882222, BE068993, BF946124, AA493841, AW169469, AI251576, AI821901, BE044000, AI701898, H86399, H47461, AI338426, AI926093, AC009086.5, AC003007.1, AF001549.1, AC004638.1, AC018868.4, AC008747.5, AC090527.3, AL050318.13, AC078846.2, AC006254.10, AL035462.21, AL355476.12, AC026431.3, AC087091.1, AC005245.1, AL031311.1, AL136981.22, AL391241.21, AC010422.7, AC010267.6, AC011609.9, AC006538.1, AC006483.3, AL353807.18, AL049776.3, Z98200.8, AC067722.21, AC010913.9, AC008622.5, AC018828.3, AL080317.11, AC005484.2, AC022383.3, Z97989.1, AL117258.4, AC004531.1, AL121594.6, AL161656.20, AL122020.5, AL157372.18, AC067742.5, AL021453.1, AL390074.17, U47924.1, AC005077.5, AC002404.1, AC008482.5, AL035404.20, AL136124.10, AC005519.3, AL359983.7, AC005932.1, Z74739.1, AL034402.9, AC004813.2, AL136304.10, AC007386.3, AC022392.4, AL136979.16, AL031660.16, Z83844.5, AP000279.1, AC004975.2, AC011462.4, AL139809.16, AL450226.1, AC007193.1, AC008812.7, AC025588.1, AL445212.9, AL121890.34, AC011497.6, AC008752.6, AP000688.1, AC007216.2, AL356915.19, AP000106.1, AF207550.1, AC016742.10, AC005620.1, AC022384.4, U95742.1, AC004000.1, AL117381.32, AC011479.6, AC007285.3, AC008484.5, AC005755.1, AL157838.24, AC023790.21, AL162724.16, AC011487.5, AC000353.27, AL137077.31, AL031733.3, AL445490.6, AC025165.27, AC018711.4, AL354707.17, AC006251.3, AP000038.1, AL590763.1, AF129756.1, AP002852.3, AC005602.1, AC010170.3, AC005041.2, AL050302.2, AC005821.1, AC004846.2, AC003041.1, AL133238.3, AL031575.1, AC005257.1, AL137918.4, AC007163.3, AP000555.1, AL135905.6, AC020915.6, AP000047.1, AC025280.4, AL117330.6, AL135927.14, AC007227.3, AL049868.20, AL133367.4, AC007686.5, AC005365.1, AC006511.5, AL163203.2, AC020928.6, AC007298.17, AC009756.9, AC005666.1, AL359091.10, AC006515.7, AL139353.3, AL136170.12, AC009238.4, AL353804.22, U91323.1, AL160236.4, AL450224.1, AL159997.14, AP001724.1, AC006452.4, AL158830.17, AC004812.1, AC007751.3, AC004675.1, AL080243.21, AJ246003.1, AL354932.26, AC009488.5, AL391987.15, AP000213.1, AL354935.23, AL158813.16, AP000744.4, AC002543.1, AC010271.6, AL138878.10, AP000558.1, AC009144.5, AL020997.1, AC004913.2, AC008392.6, AL133246.2, AL161436.12, AC073073.2, AC012306.11, AC020914.7, AC090942.1, U52112.1, AL110115.38, AC004491.1, Z96074.4, AP000135.1, AC005410.2, AJ009616.3, AF165926.2, AL121886.22, AL109628.5, AL109743.4, AC008760.6, AL078477.5, AC004534.1, AL357052.15, AC006077.1, AC008745.6, Z98752.16, AP000692.1, AC009077.7, AP000031.1, Y18000.1, Z98051.6, AC002418.1, AC008687.4, AC005920.1, AC004234.1, AC012476.8, AL513043.7, L44140.1, AL136305.14, AC010605.4, AL022323.7, AC004825.2, AC013436.5, AL138752.5, AL132712.4, AL359092.14, AC018758.2, AC011510.7,

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HSNMC45	165	1352201	1 - 573	15 - 587	AA377442.
HSQFP66	166	460537	1 - 463	15 - 477	BE465277, BF593260, AI765036, BE181153, BE181155, AA834498, BF365438.
HSRFZ57	167	892171	1 - 1916	15 - 1930	AC006159.3, AF125348.1, AC084730. 2.
HSUBW09	168	413246	1 - 1007	15 - 1021	AI991103, AI765351, AA703513, BF939824, AI925701, AW295389, AW976578, AI199421, AI422698, AI934983, BE501421, AI127932, AA703493, AW297092, AA677025, AA848037, AA814098, AW404152, AW904298, AW182186, AW197850, AA741121, AA651794, AI678148, AA906044, F18680, AA743764, AI632270, AW590435, BE045258, AA608892.
HSVBU91	169	596868	1 - 713	15 - 727	AW839808, AA077633, BF919965, AC008171.3, AF041056.1, AC004089.25, AC005081.3, AC005015.2, AB006629. 2.
HTAEE28	170	1018291	1 - 1327	15 - 1341	AW195720, AI765273, AI817356, AI928166, AI283845, BE503396, AW081502, BE349083, BF059350, AA419437, AA758800, AW206944, AA933673, AW104261, AI627565, AI264565, AW469909, AA845240, AA332515, AL021453. 1.
HTECC05	171	1352365	1 - 825	15 - 839	AA437009, AI806582, AI040972, AA442839, AA759268, AI214390, AI799076, AA918443, AW195596, AA910234.
HTEEB42	172	206980	1 - 1008	15 - 1022	AL522795, AA725566, AI421450, AL522796, AI199779, AA406389, AA912674, AW022835, AI952846, AI123727, BE218057, AW022646, N90730, BF846982, BF845761, AI652914, BF056970, AW020783, AI312805, AW393829, AI017553, AW393887, AW474261, AW264246, BF848293, AI366088, AI418268, T89217, AI052637, AW082343, BF221504, AW593293, AA865038, AI201753, BF091146, AI140139, AA987434, AA410345, BF846977, BF846980, AW900593, BF932982, BF932991, AW865421, AW136481, AI650503, AI432092, T89127, AA974715, AW261924, BE938414, AF255910.1, AY016009.1, AP001694.1, AP000087.1, AP000225.1, AP000226.1, AP000086.1, AP000223. 1.
HTEFU65	173	543396	1 - 1014	15 - 1028	AW072387, R83559, AI924465, AI364031, AW513660, BF361111, AA705541, AL162032. 1.
HTELP17	174	836072	1 - 794	15 - 808	AW976593, AW275003, BF103848, AA744857, AI458735, AW013800, AA453589, AI684921, AI184517, AI376535, AA621297, AI970221, AW015543, AA969112, AA992291, AA442130, W01308, H72782, AL519628, AA129060, AA460996, AA721433, BF665557, BE170715, AA460649, BG035897, H72781, AI382100, BF541499, AW800324, AI806305, BF885871, AI868710, AI241242, BE386136, AV723953, R75918, N75771, AI865320, AI355277, AI500061, AW088944, AI491842, BE544111, AI866469, AW007955, AI800464, AI335426, AI348777, BE891834, BG179438, AW409772, AL037582, AL037602, AV758017, AV712838, AV713988, AI536563, H42557, AV713143, AV755673, AV702147, AI174799, BE881061, BF814357, BF797305, AV721644, AI345010, AW021717, BG029829, BF793891, BF909758, AI538817, AW827289, AL037454, AW025279, AA766104, AV717730, AI817523, AL046942, BG001293, BF969354, AI554818, BE887537, AI583032, AI473536, BE789373, AI582932, AI590043, AV714010, AV717397, BG121959, AV706915, AV706624, AW027374, AA744531, AV703585, BF924856, AI819545, BE883591, AW196078, AI811631, AL036705, AI929108, BF997967, AI345745, BF921291, BE964497, AI279925, AI873638, BG029053, AI923989, AI288152, AI305745, AI539800,

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					BC004960.1, AB049849.1, AL136640.1, AB047623.1, AK024747.1, BC002409.1, AK025375.1, AF232009.1, AF217987.1, AK025092.1, AK025491.1, AL080162.1, BC003548.1, BC002473.1, AK000647.1, BC002844.1, AY033593.1, AL137480.1, AK026506.1, AL162004.1, AK024546.1, BC007499.1, BC005002.1, BC008673.1, AL512718.1, AB060897.1, AK027161.1, AF202636.1, BC000090.1, AF061795.1, AK026452.1, AF151685.1, AL136754.1, BC003684.1, AF260566.1, AK000391.1, AL353956.1, AL136586.1, BC005997.1, AL136784.1, AL133560.1, AK026408.1, BC007053.1, AK024588.1, AK027096.1, BC006091.1, AL357195.1, AF218014.1, AK025857.1, AB060879.1, AK026749.1, AK000257.1, BC007680.1, AL137558.1, AL583915.1, AL117432.1, AL389982.1, S78214.1, AK024992.1, AB051158.1, AL389939.1, BC003614.1, AJ299431.1, AK027082.1, BC002357.1, AF141289.1, AK026947.1, AB048954.1, AB048975.1, AL110221.1, AL096744.1, AB060914.1, AK026631.1, AK026542.1, BC007326.1, AB050407.1, AL136850.1, AB060893.1, AF132676.1, AB060873.1, AF061836.1, AL117583.1, AL137648.1, AL512733.1, AL390184.1, AL137711.1, AB060888.1, AL110158.1, AF090900.1, AF274348.1, AF036268.1, AF274347. 1.
HTELS08	175	847090	1 - 1884	15 - 1898	AW664990, AA608835, BE972717, AA383680, AW572898, AI028204, AI554902, AI138881.
HTLEP53	176	634852	1 - 804	15 - 818	BF876683, AI755202, AI066646, AW613805, AA084609, AW769151, BE169870, AA601674, AI561210, BF926568, AW265614, BF826830, AI613389, AL042667, AL042670, AW130427, BF868994, AW471092, AV760019, AW576485, AI281818, AA225956, N64587, AU157209, BF941382, AI340151, AI859834, AW328202, AV754716, AW501278, BG222269, AI955029, AL134440, AI799569, BG250286, AW518030, AW576437, BF725884, BE396138, AW974363, T05118, AA524616, AI732682, AW268329, AI192440, AA669741, AW166920, D58782, AI653493, AW238341, BE301068, AI955718, BF923179, BF526964, AW438850, AW438662, U95742.1, AC019205.4, AC027125.4, AL356299.16, AC007216.2, AC008649.6, AC005484.2, AC005098.2, AC005740.1, AB020868.1, AC008569.6, AL359091.10, AL136527.9, AC005527.3, AC005000.2, AC005529.7, AL121809.6, AC090883.1, AC006312.8, AC004166.12, AF250325.1, AL008726.3, AL139396.17, AC010913.9, Z85987.13, AL590762.1, AL121658.2, AJ246003.1, AP001781.4, AP001694.1, AC004867.5, AL133312.3, AL513550.9, AC008507.8, AL022476.2, AC005520.2, AC068533.7, AL160163.24, AC011485.6, AF111167.2, AC002544.1, AC004702.1, AL158141.14, AC005071.2, AC007191.1, AC005229.1, AL357515.26, AC010412.7, AL161670.4, AF196972.1, AL135927.14, AC007227.3, AC083884.6, AC004089.25, AL445483.13, AF165926.2, AC009060.7, AL359235.3, AC002350.1, AC005952.1, AC007052.4, AC020558.4, AL035071.17, AP000510.2, AC007731.14, AL121586.31, AL354815.10, AC005500.2, AC006014.2, AC005015.2, AL161893.24, AC005726.1, AC004985.2, AL161725.13, AC002390.1, AL450265.11, AL353135.32, AL160231.4, AC026672.44, AC004466.1, AC060231.6, AL360227.17, AL117382.28, AL021397.1, AC083863.2, AC011487.5, AL158824.11, AC018638.5, AL031283.26, AL121761.5, AC004242.1, AL020993.1, AL512641.9, AL121936.17, AC005280.3, AL035587.5, AC020916.7, AC067941.7, AC009812.17, AC012476.8, AL136228.8, AP001728.1, AL354808.24, AL049561.16, AL352984.4, AP000046.1, AC010378.6, AC000381.1, AC006480.3, AC006023.2, AL050308.9, AC005531.1, AL049776.3, AP000114.1, AC008551.5, AL031680.20, AL391827.18,

					AP001360.4, AL354707.17, AF111168.2, AL031683.2, U89337.1, AC010605.4, AL035367.5, AC002546.1, AL138724.12, AL033521.2, AC020906.6, AC078846.2, AC006452.4, AC007003.4, AC009244.24, AL049547.10, AL163279.2, AF064861.1, AC000025.2, AC027319.5, AL391280.15, AC008083.23, AC004253.1, AC008598.5, Y10196.1, AL049766.14, AL512666.6, AL138784.30, AC008891.7, AC004840.3, AC083873.3, AC005377.2, AC000360.35, AL049637.43, AL512378.7, AC008753.8, AC005488.2, AF001548.1, AC010422.7, AC009179.17, AC008623.4, AC004876.2, AP001717.1, AP001709.1, AC011465.4, AP000901.5, AL160471.5, AC006329.5, AL034405.16, AC008521.5, L44140.1, AC008481.7, U15177.1, AL162578.13, AC006449.19, Z97876.1, AC016830.5, AC008946.6, AL137792.11, AL109743.4, Z83844.5, AL049631.7, AC025275.4, AC091736.1, AP002453.3, AC006512.12, AC004491.1, AL356095.11, AC005291.1, AL136297.3, AC003982.1, AL022318.2, AC009086.5, AC005736.1, AC004824.3, Z84466.1, AP001670.1, AL157823.9, AC018904.6, AC002425.1, AF312032.1, AL109806.22, AL035413.19, AC006027.1, Z84469.1, AL513366.11, AC011737.10, AF196779.1, AC026756.15, AC008745.6, AC090527.3, AC006038.2, AC005318.1, AL391137.11, AC010543.8, AC005081.3, AC005522.2, AC005231.2, AC013726.7, AL109804.41, AC005399.19, AC004832.3, AC022148.5, AF134726.1, AC022007.3, AP002851.2, AL136084.11, AL031295.1, AP001748.1, AL121834.20, AC007686.5, AL049872.3, AL049569.13, AC016993.4, AC004805.1, AL133551.13, AL136966.27, AC004167.1, AP000237.1, AL117186.3, AL161747.5, AC005288.1, X54156.1, U94788.1, Z99127.1, AC016691.10, AC016025.12, AC010526.7, AC004890. 2.
HTPCS72	177	854941	1 - 3421	15 - 3435	AV716024, BF032601, BE884480, BG107409, BE896847, AA534380, BF996760, BE935961, AA625472, BF593809, AI275974, AA758011, AI091865, AA770655, AA826573, AA642458, AA284480, AA308157, BF316735, AA150509, AI338707, H98214, AI085686, AI613457, AW007656, BE677803, BE092569, AW083271, BF890758, AA156713, BF315290, BF687549, AI079204, R38877, AI561066, AW629504, Z44870, AI638057, AA468549, BF445676, AW771735, BF852685, AW173317, BF882397, BE092420, AA368918, AW969242, AI254739, T80580, AA406249, F07793, R55262, R12721, BE832360, R55263, AW900776, BF357645, F05814, Z40638, F04054, AA321781, AW021358, AA714089, BF886411, BE149465, H91564, AA954780, BF871030, AI640665, BF036620, F02061, AA243079, BF307290, BF835491, BE774931, H90643, N44003, AA307326, AW135695, BE927559, AA242996, BF757045, AW999558, AI002239, BE567146, D19832, AW672798, BF089866, W73266, AF017388, BE932984, BE832354, BE707285, AB040946.1, AL008639.15, AF139898.1, AK027079.1, AF131746. 1.
HTPIH83	178	919916	1 - 1467	15 - 1481	BE513091, BE304667, BG164062, AW385836, AW837727, AW837724, BF032123, BF541534, AW006504, AI769564, AW837723, AA552647, AW015998, AI343787, AI285131, AA976345, BE048787, AI949846, AI685788, AI953481, AW083920, BF819923, AI262767, AW194732, AA345449, AA639438, T86266, AI469683, AI244378, AI659323, T86158, BF758311, BG164241, AI932964, AV647382, BF104997, AI913916, AF177340.1, AL158821.16, AF250558. 1.
HTSEW17	179	460579	1 - 638	15 - 652	AA779073, AI860913, AI028060, AI024955, BE549714, AW136463, R07163, AW612172, BF773051, AF007146.1, AF381980. 1.
HTTBI76	180	637725	1 - 1697	15 - 1711	AA059411, BE568135, BE856883, BF435859, BF977217, AV701624, BE566398, BE856637, AA429722,

					BE564953, BE568948, BF214557, AA196423, AW237471, AA716665, AI377511, AA193289, N51319, BF248318, AI796263, AI770155, AA045194, BE380112, BF029088, AI185077, AA442760, BF214729, BE865742, AA810811, AI572127, AI494075, BE777718, AA128609, AA933879, BF027898, BF691014, BF977570, AV702879, AA421072, N63065, BE866018, AI373224, R99289, BG003427, BE568709, AA919169, AI580336, AW024454, BF057794, AA731146, AA128610, BF105164, AA062583, BF031391, BE866602, BF238619, AI758175, AA045378, D61992, BF211153, R99375, AA420992, AA194235, AA976350, AW135598, AI648675, BF436083, BE392607, AA383499, BF368270, AA878813, AA877180, BE379677, AI219249, AA846496, AV760348, AA380012, BE866426, AA453722, BF687711, BF213063, H84990, H86604, H86921, AL519369, AA383353, BE742087, AA007586, T85467, BE514581, BF573588, BF028113, AL521923, BF091941, BE548812, AI244008, H55168, AA379174, BE621508, AI200967, BF346162, AL137861.5, AC005690.8, AF277188. 1.
HTTBS64	181	100815 9	1 - 2044	15 - 2058	AW801486, AL157701.2, AC006356.3, AC079033.12, AC025159.28, AL360078.16, AF002997.2, AL034428.4, AP001693.1, AL049873.3, Z83819.1, AL389889.11, AP001669.1, AL035552.9, AL590043.7, AC005406.2, AC009069.3, AC048346.13, AL354937.12, AL050401.5, AL136324.6, AL390800.4, AC073941.5, AP001597.1, AC012464.24, AC008277.4, AL121985.13, AC004988.2, AL359085.14, AC016623.5, AL163213.2, AL359850.7, AL357894.6, AL133247.1, AF003528.1, AC090946.1, AL021877.1, AL157779.6, AL137245.11, AC008250.23, AL031391.1, AL355530.6, AL589740.4, AL354750.12, AC002076.1, AL139090.11, AL354896.16, AC021863.5, AL121577.1, AL049732.11, AC012003.9, AL117259.6, AC010144.4, AC068061.5, AC068800.28, AL512452.7, AC010142.4, AC026691.4, AL354802.15, AL359252.17, AL512662.8, AC008506.7, AL022718.1, AC008462.6, AL356499.16, AL359332.2, AC019196.10, AL138479.4, AL137061.12, AP001331.1, AC019179.4, AL450333.13, AF003529.1, AL133444.4, AC034195.6, Z98753.1, AL161630.12, AL359273.11, AC005799.1, AL390247.11, AL392087.7, AL078594.36, AL139087.13, AL359999.11, AC004216.1, AC007543.4, AL033522.1, Z99571.1, AC012405.5, AL390959.12, AL160236.4, AL138773.4, AC079457.14, AC007158.10, AL359636.17, AC006979.2, AC002302.1, AL445687.5, AC005873.3, AC023095.7, AL136100.12, AC007214.13, AL162500.15, AC004160.1, AP001533.4, U82828.1, AC073273.9, AL034369.1, AL445985.10, AC006351.3, AC002065.1, AC022081.32, AL158053.14, AC010591.8, AC005284.1, AL355578.4, AC010534.7, AC005249.1, AC009466. 17.
HTXJM03	182	603918	1 - 2384	15 - 2398	AL518347, BE742019, AI114655, BF514929, AL118845, BF880731, AA236989, AI140989, AW813468, BE841331, AW582445, AA252594, AA618239, AI823453, AI280443, BF988837, AL042692, BF989072, H15090, AW391644, BG011632, H15570, Z43079, H15630, AW813319, H22799, Z39170, AA252414, F07601, F11156, F05157, AA746494, H15091, F08825, W68008, AW813329, F03848, F01404, AA804351, AC005829.1, AB033093.1, BC006271. 1.
HTXON32	183	838288	1 - 1491	15 - 1505	AA746911, AA410788, AA704393, AA181917, BG222813, BE301584, AA683069, AA507822, AI056177, AA228778, AA084609, BE178231, BE178064, AI678867, AU147162, AV747362, AI857836, BF821968, AI754170, AW769654, AA825827, AA468975, AW513071, AW328202, AW069412, BF950533, AI962030, AI188049, BG250286, AI915075, BG222564, BG222326, AV733824, AV759632,

					AA584862, BE246405, AK000114.1, AL035088.1, AC003691.1, AP001359.4, AC004605.1, Z94056.1, AC010422.7, AC004125.1, AC012157.20, AC007912.6, AC005368.1, AL031257.1, AL354680.14, AC079353.5, AF130417.4, AC005011.2, AP001672.1, AC005255.1, AL445071.14, AL354977.10, AC006013.3, AP000851.4, AC008945.6, AC003689.1, AC002288.1, AC006211.1, AP002751.3, AL133391.5, Z98200.8, AF001905.1, AC006597.2, AC012450.9, AC005840.2, AC008699.5, AC007934.7, AC002422.1, AP000347.1, AL162831.5, AC009408.3, AC026191.3, AL136992.22, AC007436.1, AL590381.4, AC008840.4, AL008721.1, AC005841.3, AC021325.5, AL451061.8, AL117382.28, AC008511.6, AC004846.2, AL355365.10, AC004531.1, AC007652.1, AP001972.4, AP001727.1, AC087237.14, AC010465.7, AL157877.11, AL355984.11, AC010601.5, AL356095.11, AC004916.2, AC008264.10, AC025457.5, AP001561.4, AP000008.1, AC018719.4, AC007773.1, AC009094.7, AC010234.5, AC011890.4, AL355812.23, AC025471.5, AC020913.6, AP000704.2, AL135905.6, AC021863.5, AC022087.8, AC004659.1, AL022329.9, AC027342.4, AC019212.4, AC017100.4, AC020928.6, AC004104.1, AC019184.3, AL160274.9, AL161899.21, Z82194.1, AC026811.4, AC015842.9, AC002420.1, AL035079.14, AL390239.16, AC008012.8, AP001691.1, AL138819.9, AC009142.10, AL512449.6, AC024028.10, AC079408.25, AC005015.2, AL451126.18, AF011889.1, AL032821.2, AC004999.1, AF131216.1, AL109963.4, AL021939.1, AC008474.7, AC004089.25, AL391666.5, AL353135.32, AC005081.3, AF001551.1, AL096699.11, AC012312.8, AL031657.5, AL158832.13, AC006030.2, AL355336.15, AL050320.19, AC002553.1, AC005480.3, AF017104.1, AP001825.4, AC009779.18, AC016554.7, AC037433.6, AL033519.42, AC006313.1, AC019050.4, AL109623.9, AC012150.16, AL138749.13, AP000067.1, AL132994.4, AC004491.1, AC007993.15, AC025165.27, AF196970.1, AL157817.13, AC002377.1, AP000495.1, AB020869.1, AC009224.6, AC010582.6, AL160397.17, AL136040.5, AC068513.7, AL133173.19, AC004057.1, AC004616.1, AL353777.18, AP003473.2, AC008958.6, Z97635.10, AC073057.6, AC008427.7, AL137790.4, AC006316.2, AC005537.2, AC067941.7, AL035604.15, AC004021.1, AL035462.21, Z84480.1, AC003009.1, AC016778.3, AL355312.24, AC005746.1, AC005768.17, AC003690.1, Z97054.1, AP000577.4, AC069292.12, AL138696.16, AL354799.12, AL158828. 14.
HUFCJ30	184	638402	1 - 854	15 - 868	AL533274, AI741266, AA194264, BF438670, BE855763, AI912191, BF109379, AI815187, AA521107, BE646628, AI911233, AA828445, AA429411, AI912933, AI423970, AI242299, BE042993, AW276617, AA905840, AA464614, AI394374, AW340805, AI096492, AI221797, AW129415, AI554269, AW969178, BG055418, AW029033, AW044596, AA582358, BE882568, AI870051, AA233165, AI933519, AI370473, BE676140, AW292630, AA429458, F03916, AA233241, F03174, AA193481, H61820, AA193313, AW080606, AL533316, AA442046, AW975876, AW971403, AW974801, AW976024, AW975037, AW971975, AW972292, AW975965, AW975031, AW975002, AW971404, AW975019, AW975952, AW979127, AW974786, AW975105, AW975032, AW974964, AW979238, AW971968, AW975930, AW975954, AW969673, AW979090, AW975154, AW979002, AW969727, AW976023, AW975434, AW979204, AW969680, AW969643, AW974806, AW979098, AW975942, AW975971, AW973213, AW979176, AW973717, AW971326, AW974658, AW973219, AW969885, AW974338, AW971375,

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HUVEB53	185	571200	1 - 1488	15 - 1502	BE786669, AA453165, BG027754, AI694207, AW751021, BE140357, BE140309, BF673837, AI827679, AI597942, AI831626, BF572868, AW131344, AV726756, BE844218, BE162515, AA188243, AW188015, AW044629, AA877403, AI127993, BF691063, AA989288, AA453945, AA191206, AV748508, AA481849, AA405313, BF670519, AI167809, AA431686, AA846755, AI041097, AA305896, BE844200, BE844214, AI160824, H13901, AA655009, R68945, W26226, AA861877, AW974213, H11654, AW953548, AA453440, AI587514, AI076451, AA405350, H04206, AW751099, AA855040, AA974088, H43741, Z33442, AA825311, AA036965, AA188839, BE844205, H04207, AA923377, AA903946, AV693909, BE968480, AA761680, AV724398, AV724896, AA352991, AA330417, AA887483, D57665, N51756, AA206627, D61904, BF440004, AI248842, H58383, AA975213, D79380, AA205353, BE785631, AA344562, AA864363, D61991, BE467097, AA773771, AA649813, AW592162, AA642834, D79365, N47004, AW900901, AA036966, D61899, D58112, AA579902, AA865874, AA722600, R68832, R40852, H45338, BF131609, AA007516, H13852, AI828027, AA431480, BE149422, AV686924, AW074757, D20526, AB032988.1, AL021396. 8.
HWAAD63	186	838626	1 - 3294	15 - 3308	BG058664, AW953071, BF668217, AL046409, AI284640, AW406162, BF852604, AU123691, AL046205, AW303196, D82290, AW301350, AI334443, AV761286, AL121235, AW274349, AW600804, BF339640, BF677892, AV763892, BG032943, AI572924, AI801482, AI431303, AL044940, AV740801, AV764490, BG249643, AV762098, AI270117, AW969629, AI732378, AW265385, AI963720, AI708009, AI350211, AU147104, AW473163, AA669840, AV735495, AI149478, AV763971, AA581903, AV759518, AV760937, AI754955, AL041690, AI583283, AV710066, AV763550, BG236735, AU145314, AW502975, AV742057, BG167743, BF940837, AW193265, AV760777, BF914859, BF918590, AF074667, AV763122, BF918640, BE908796, BG036337, AW513362, AA491814, AV759362, BF725315, AV762050, AV763354, AW021583, BF919090, AI203955, AA531580, AA613232, AA490183, D82542, AW576391, AI623720, AV739452, AV728425, BE350475, AW500125, AA521323,

					AA665330, AV702857, AV730391, BF347791, AA610491, T40452, AA584167, AW474160, AI613280, AV762139, BE253048, AI192631, AI732865, AW020992, AA938105, AV733830, AF074677, AV652936, AW276817, BE872393, AW088846, AW438643, AI434695, AI345654, AW270270, AI610159, AW274346, AW265170, BF680041, BF854876, AA469451, AI589230, AA584145, AW833862, BE047069, AI570261, BF347740, AI619997, AW264934, AL042420, BF475381, AW518220, BF942454, AV762009, AI708125, BF697673, AW148792, BE297262, AW731867, AV759505, AA457542, BF991286, BF806176, AV728410, AU159337, AW089322, BE164494, AA774222, AI345518, AW963497, AV763255, AI696962, AL041706, F36273, AA496508, AV764228, AA478355, AV713243, AV761613, BE677379, BF736198, BF916517, AW079135, AV735370, R99597, AA652764, AW029038, AV725423, AA410828, AW169517, BG250302, AV761786, BE393367, BF872630, AF063563, AV764241, AA601294, BF827410, BF812839, AL119691, AV760378, AA177061, BG177715, BF674620, AI298710, AW169151, AA502104, AI345681, AI345675, AA633798, AV761925, AA682912, BF965007, AV733710, BF680074, AV762768, AA579362, BE139146, BF217299, AV762111, AV764578, AL118559.6, AB038653.1, AC020904.6, AC009497.3, AC006581.16, AF001549.1, AC004638.1, AC008267.6, AL121601.13, AL109865.36, AL356915.19, AC018809.4, AL163973.1, AC023908.6, AC011465.4, AL160237.4, AP000459.3, AC005081.3, AC044797.5, AC009154.5, AP001760.1, AL035367.5, AC007298.17, AL139350.17, AC006329.5, AC004019.20, AC006038.2, AC011455.6, AC008616.6, AL354932.26, AC011461.4, AL161892.9, AC005911.6, AC008265.15, U80017.1, AP003357.2, U91323.1, AC018636.4, AC005562.1, AL096701.14, AL080243.21, AC011450.4, AL133367.4, AL162458.10, AL354720.14, AC020658.6, AL158830.17, AL050318.13, AC005839.1, AP001687.1, AC009144.5, AC005041.2, Z99495.1, AC002565.1, AC022007.3, AC018769.2, AP000031.1, AC008372.6, AC011811.42, AC008688.7, AC009298.3, AP000047.1, AL445222.9, AL163248.2, AL139113.21, AC006435.7, AL136219.17, AC011495.6, AC008562.4, AC022308.17, AC008537.5, AP001667.1, AL133399.1, AL353135.32, AL121809.6, AC005696.1, AC073838.6, AC002476.1, AC006028.3, AP000115.1, AL445928.8, Z69666.1, AC005522.2, AC084783.2, AL133485.3, AC016025.12, AC004906.3, AC008649.6, AP000553.1, AC009470.4, AL031054.1, AC007193.1, AP000338.2, AL117334.29, AC009530.5, AP001346.1, AL034380.26, AC016830.5, AC008403.6, AL049550.5, AC027644.9, AC011930.5, AL109965.34, AC006241.1, AL049869.6, Z83844.5, Z98941.1, AL031283.26, AL159191.4, AP000216.1, AC009996.7, AC015842.9, AL136295.3, AL139330.17, AC008745.6, AC005527.3, AC007731.14, U47924.1, AC012377.5, AC025212.5, AC005500.2, AC018751.30, Z93241.11, AL078638.9, AL354993.24, AC016769.10, AC005324.1, AL355517.12, AC074121.16, AC012170.6, AC006538.1, AP000962.2, AC004650.1, AC083884.6, AL354935.23, U52111.2, AC016027.15, AC079363.19, AP000113.1, AP000045.1, AL136123.19, AC007011.1, AL357150.7, AC008753.8, AL121675.36, AC002551.1, AL157838.24, AC009516.19, AC004865.1, AL139230.25, AC005529.7, AL050335.32, AC007216.2, AL049759.10, AP001716.1, AL021546.1, AC000360.35, AP001718.1, AE006639.1, AC025436.2, AL359091.10, AC004940.1, AC008101.15, AC003029.2, AL352978.6, AC020983.7, AL118520.26, AC007272.3, AC005154.1, AC078878.20,

					AL136980.5, AC005778.1, AC004971.3, AL033383.26, AC005921.3, AL159995.8, AC008068.4, AL008718.23, U95742.1, AC068712.6, AL024474.1, AC005031.1, AC017091.8, AC090514.1, AP001666.1, AL158040.13, AL161799.19, AL133387.8, AC003108.1, AC005808.1, AL109825.23, AC004033.3, Z98051.6, AC005295.1, AL353764.9, AC011236.8, AL132768.15, AC006285.11, Z99716.4, AL139396.17, AL096840.25, AL022098.1, AC005052.2, AC002300.1, AC007066.4, AL109797.18, AC004686.1, AL031662.26, AC008812.7, AL161656.20, AL136961.19, AC007404.4, AC020550.4, AJ003147.1, AP001858.4, AC021203.5, AC011559.3, AL117258.4, AC007620.30, AC010553.6, AP002028.1, AL356575.8, AP000299.1, AL121748.6, AL136300.22, AC016257.22, AC003684.1, AC004941.2, AL157406.19, AL049694.9, AL162853.17, U66059.1, AC026464.6, AL121972.17, AC013264.4, AL162426.20, AC006345.4, AC090960.1, AL049742.7, AC005037.2, AP000359.1, AC007051.3, AC018633.2, AL133174.15, AC008474.7, AC018635.6, AB023049.1, AC034198.6, AC022211. 5.
HWADJ89	187	799506	1 - 1755	15 - 1769	AW958273, AW377130, AW574767, AW138853, BF111962, AA135712, AA156931, AW264402, AW117200, AI684896, AW339989, AA524553, AI394626, AI754796, AI860485, AI989549, AW129957, AI672796, BG056354, AA040909, AI000898, AI421190, AI693729, AW512733, AW044450, AI090274, AW205364, AW081734, BE939287, N35410, AA788655, N55117, AA844145, AI091868, N62863, AW302517, AI361489, AI628038, AA765992, AI800010, AI817849, BF800164, AI285397, AW403436, AA658416, AA648845, F13408, N73777, AA983941, R34886, AI024148, T04873, AA310563, Z33435, R72500, AI219780, AI149773, BG248348, R49268, BE305119, BE293618, AI743430, AW440724, T78828, BE249965, F10993, BE250024, AI371489, BE171979, N77769, AW235832, AI204426, R34492, N48042, BF899137, BF842700, R34372, Z38685, N99398, AI857456, AW841803, BE176205, AW899803, AA665233, AI290874, AW591407, AI432644, BF757092, AI623302, AW968355, AI431347, AI432653, AW081103, AI431230, AI431328, AI432654, AI432655, AI431310, AI431312, AI432650, AI432677, AW968356, BE672759, AI431353, AW971740, AW972091, AW972093, AW968729, AI431307, AI431316, AI432661, AI431354, AI431315, AI431337, AI431257, AI492519, BE672745, BE672732, AI791349, AI432666, AI432675, AW128900, BE672748, AI431238, AI492520, BE672719, AI432651, AI432647, AI431330, AI432674, AI432672, BF448552, AW972092, BE672767, AI431243, AI431248, AI432665, AI432657, AI432658, AI432649, BE672644, AI431255, BE672774, BE672742, AW969229, AI431254, BF589777, AI431350, AI431231, AI432662, AI431345, BE672738, AI431357, AW858522, AI431241, AI431351, AI431323, AI431346, AI431247, AI431318, AI432676, AI432673, AI431235, AI431321, AW128897, AI431340, AI432643, BE672792, AW128846, AI432664, AI431246, AW972090, AI432645, AW128884, BE672743, AI492510, BE672640, AL042931, AI431314, AW129223, AI431308, BE672749, BE672744, AI492509, BE672622, AI431751, BE672627, AL042729, AL045494, AL042655, BE672626, AL042523, AL042519, AL042853, AL031296.1, AK026719.1, AB007922.2, AF052104.1, AF064854.1, AL133082. 1.
HWBFX31	188	799427	1 - 1663	15 - 1677	H93613, N75773, N22551, AA884923, AW873751, H93612, AC039057. 8.

Description of Table 4

Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1B.2, column 5. Column 1 of Table 4 provides the tissue/cell source identifier code disclosed in Table 1B.2, Column 5. Columns 2-5 provide a description of the tissue or cell source. Note that "Description" and "Tissue" sources (i.e. columns 2 and 3) having the prefix "a_" indicates organs, tissues, or cells derived from "adult" sources. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease." The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector use d to generate the library.

Table 4

Code	Description	Tissue	Organ	Cell Line	Disease	Vector
AR022	a_Heart	a_Heart				
AR023	a_Liver	a_Liver				
AR024	a_mammary gland	a_mammary gland				
AR025	a_Prostate	a_Prostate				
AR026	a_small intestine	a_small intestine				
AR027	a_Stomach	a_Stomach				
AR028	Blood B cells	Blood B cells				
AR029	Blood B cells activated	Blood B cells activated				
AR030	Blood B cells resting	Blood B cells resting				
AR031	Blood T cells activated	Blood T cells activated				
AR032	Blood T cells resting	Blood T cells resting				
AR033	brain	brain				
AR034	breast	breast				
AR035	breast cancer	breast cancer				
AR036	Cell Line CAOV3	Cell Line CAOV3				
AR037	cell line PA-1	cell line PA-1				
AR038	cell line transformed	cell line transformed				
AR039	colon	colon				
AR040	colon (9808co65R)	colon (9808co65R)				
AR041	colon (9809co15)	colon (9809co15)				
AR042	colon cancer	colon cancer				
AR043	colon cancer (9808co64R)	colon cancer (9808co64R)				
AR044	colon cancer 9809co14	colon cancer 9809co14				
AR050	Donor II B Cells 24hrs	Donor II B Cells 24hrs				
AR051	Donor II B Cells 72hrs	Donor II B Cells 72hrs				
AR052	Donor II B-Cells 24 hrs.	Donor II B-Cells 24 hrs.				
AR053	Donor II B-Cells 72hrs	Donor II B-Cells 72hrs				
AR054	Donor II Resting B Cells	Donor II Resting B Cells				

AR055	Heart	Heart				
AR056	Human Lung (clonetech)	Human Lung (clonetech)				
AR057	Human Mammary (clontech)	Human Mammary (clontech)				
AR058	Human Thymus (clonetech)	Human Thymus (clonetech)				
AR059	Jurkat (unstimulated)	Jurkat (unstimulated)				
AR060	Kidney	Kidney				
AR061	Liver	Liver				
AR062	Liver (Clontech)	Liver (Clontech)				
AR063	Lymphocytes chronic lymphocytic leukaemia	Lymphocytes chronic lymphocytic leukaemia				
AR064	Lymphocytes diffuse large B cell lymphoma	Lymphocytes diffuse large B cell lymphoma				
AR065	Lymphocytes follicular lymphoma	Lymphocytes follicular lymphoma				
AR066	normal breast	normal breast				
AR067	Normal Ovarian (4004901)	Normal Ovarian (4004901)				
AR068	Normal Ovary 9508G045	Normal Ovary 9508G045				
AR069	Normal Ovary 9701G208	Normal Ovary 9701G208				
AR070	Normal Ovary 9806G005	Normal Ovary 9806G005				
AR071	Ovarian Cancer	Ovarian Cancer				
AR072	Ovarian Cancer (9702G001)	Ovarian Cancer (9702G001)				
AR073	Ovarian Cancer (9707G029)	Ovarian Cancer (9707G029)				
AR074	Ovarian Cancer (9804G011)	Ovarian Cancer (9804G011)				
AR075	Ovarian Cancer (9806G019)	Ovarian Cancer (9806G019)				
AR076	Ovarian Cancer (9807G017)	Ovarian Cancer (9807G017)				

AR077	Ovarian Cancer (9809G001)	Ovarian Cancer (9809G001)				
AR078	ovarian cancer 15799	ovarian cancer 15799				
AR079	Ovarian Cancer 17717AID	Ovarian Cancer 17717AID				
AR080	Ovarian Cancer 4004664B1	Ovarian Cancer 4004664B1				
AR081	Ovarian Cancer 4005315A1	Ovarian Cancer 4005315A1				
AR082	ovarian cancer 94127303	ovarian cancer 94127303				
AR083	Ovarian Cancer 96069304	Ovarian Cancer 96069304				
AR084	Ovarian Cancer 9707G029	Ovarian Cancer 9707G029				
AR085	Ovarian Cancer 9807G045	Ovarian Cancer 9807G045				
AR086	ovarian cancer 9809G001	ovarian cancer 9809G001				
AR087	Ovarian Cancer 9905C032RC	Ovarian Cancer 9905C032RC				
AR088	Ovarian cancer 9907 C00 3rd	Ovarian cancer 9907 C00 3rd				
AR089	Prostate	Prostate				
AR090	Prostate (clonetech)	Prostate (clonetech)				
AR091	prostate cancer	prostate cancer				
AR092	prostate cancer #15176	prostate cancer #15176				
AR093	prostate cancer #15509	prostate cancer #15509				
AR094	prostate cancer #15673	prostate cancer #15673				
AR095	Small Intestine (Clontech)	Small Intestine (Clontech)				
AR096	Spleen	Spleen				
AR097	Thymus T cells activated	Thymus T cells activated				
AR098	Thymus T cells resting	Thymus T cells resting				
AR099	Tonsil	Tonsil				
AR100	Tonsil geminal center centroblast	Tonsil geminal center centroblast				

AR101	Tonsil germinal center B cell	Tonsil germinal center B cell				
AR102	Tonsil lymph node	Tonsil lymph node				
AR103	Tonsil memory B cell	Tonsil memory B cell				
AR104	Whole Brain	Whole Brain				
AR105	Xenograft ES-2	Xenograft ES-2				
AR106	Xenograft SW626	Xenograft SW626				
AR119	001: IL-2	001: IL-2				
AR120	001: IL-2.1	001: IL-2.1				
AR121	001: IL-2_b	001: IL-2_b				
AR124	002 : Monocytes untreated (1hr)	002 : Monocytes untreated (1hr)				
AR125	002 : Monocytes untreated (5hrs)	002 : Monocytes untreated (5hrs)				
AR126	002: Control.1C	002: Control.1C				
AR127	002: IL2.1C	002: IL2.1C				
AR130	003 : Placebo-treated Rat Lacrimal Gland	003 : Placebo-treated Rat Lacrimal Gland				
AR131	003 : Placebo-treated Rat Submandibular Gland	003 : Placebo-treated Rat Submandibular Gland				
AR135	004 : Monocytes untreated (5hrs)	004 : Monocytes untreated (5hrs)				
AR136	004 : Monocytes untreated 1hr	004 : Monocytes untreated 1hr				
AR139	005: Placebo (48hrs)	005: Placebo (48hrs)				
AR140	006: pC4 (24hrs)	006: pC4 (24hrs)				
AR141	006: pC4 (48hrs)	006: pC4 (48hrs)				
AR152	007: PHA(1hr)	007: PHA(1hr)				
AR153	007: PHA(6HRS)	007: PHA(6HRS)				
AR154	007: PMA(6hrs)	007: PMA(6hrs)				
AR155	008: 1449_#2	008: 1449_#2				
AR167	1449 Sample	1449 Sample				

AR168	3T3P10 1.0uM insulin	3T3P10 1.0uM insulin				
AR169	3T3P10 10nM Insulin	3T3P10 10nM Insulin				
AR170	3T3P10 10uM insulin	3T3P10 10uM insulin				
AR171	3T3P10 No Insulin	3T3P10 No Insulin				
AR172	3T3P4	3T3P4				
AR173	Adipose (41892)	Adipose (41892)				
AR174	Adipose Diabetic (41611)	Adipose Diabetic (41611)				
AR175	Adipose Diabetic (41661)	Adipose Diabetic (41661)				
AR176	Adipose Diabetic (41689)	Adipose Diabetic (41689)				
AR177	Adipose Diabetic (41706)	Adipose Diabetic (41706)				
AR178	Adipose Diabetic (42352)	Adipose Diabetic (42352)				
AR179	Adipose Diabetic (42366)	Adipose Diabetic (42366)				
AR180	Adipose Diabetic (42452)	Adipose Diabetic (42452)				
AR181	Adipose Diabetic (42491)	Adipose Diabetic (42491)				
AR182	Adipose Normal (41843)	Adipose Normal (41843)				
AR183	Adipose Normal (41893)	Adipose Normal (41893)				
AR184	Adipose Normal (42452)	Adipose Normal (42452)				
AR185	Adrenal Gland	Adrenal Gland				
AR186	Adrenal Gland + Whole Brain	Adrenal Gland + Whole Brain				
AR187	B7(1hr)+ (inverted)	B7(1hr)+ (inverted)				
AR188	Breast (18275A2B)	Breast (18275A2B)				
AR189	Breast (4004199)	Breast (4004199)				
AR190	Breast (4004399)	Breast (4004399)				
AR191	Breast (4004943B7)	Breast (4004943B7)				
AR192	Breast (4005570B1)	Breast (4005570B1)				
AR193	Breast Cancer (4004127A30)	Breast Cancer (4004127A30)				
AR194	Breast Cancer (400443A21)	Breast Cancer (400443A21)				
AR195	Breast Cancer (4004643A2)	Breast Cancer (4004643A2)				

AR196	Breast Cancer (4004710A7)	Breast Cancer (4004710A7)				
AR197	Breast Cancer (4004943A21)	Breast Cancer (4004943A21)				
AR198	Breast Cancer (400553A2)	Breast Cancer (400553A2)				
AR199	Breast Cancer (9805C046R)	Breast Cancer (9805C046R)				
AR200	Breast Cancer (9806C012R)	Breast Cancer (9806C012R)				
AR201	Breast Cancer (ODQ 45913)	Breast Cancer (ODQ 45913)				
AR202	Breast Cancer (ODQ45913)	Breast Cancer (ODQ45913)				
AR203	Breast Cancer (ODQ4591B)	Breast Cancer (ODQ4591B)				
AR204	Colon Cancer (15663)	Colon Cancer (15663)				
AR205	Colon Cancer (4005144A4)	Colon Cancer (4005144A4)				
AR206	Colon Cancer (4005413A4)	Colon Cancer (4005413A4)				
AR207	Colon Cancer (4005570B1)	Colon Cancer (4005570B1)				
AR208	Control RNA #1	Control RNA #1				
AR209	Control RNA #2	Control RNA #2				
AR210	Cultured Preadipocyte (blue)	Cultured Preadipocyte (blue)				
AR211	Cultured Preadipocyte (Red)	Cultured Preadipocyte (Red)				
AR212	Donor II B-Cells 24hrs	Donor II B-Cells 24hrs				
AR213	Donor II Resting B-Cells	Donor II Resting B-Cells				
AR214	H114EP12 10nM Insulin	H114EP12 10nM Insulin				
AR215	H114EP12 (10nM insulin)	H114EP12 (10nM insulin)				

AR216	H114EP12 (2.6ug/ul)	H114EP12 (2.6ug/ul)				
AR217	H114EP12 (3.6ug/ul)	H114EP12 (3.6ug/ul)				
AR218	HUVEC #1	HUVEC #1				
AR219	HUVEC #2	HUVEC #2				
AR221	L6 undiff.	L6 undiff.				
AR222	L6 Undifferentiated	L6 Undifferentiated				
AR223	L6P8 + 10nM Insulin	L6P8 + 10nM Insulin				
AR224	L6P8 + HS	L6P8 + HS				
AR225	L6P8 10nM Insulin	L6P8 10nM Insulin				
AR226	Liver (00-06-A007B)	Liver (00-06-A007B)				
AR227	Liver (96-02-A075)	Liver (96-02-A075)				
AR228	Liver (96-03-A144)	Liver (96-03-A144)				
AR229	Liver (96-04-A138)	Liver (96-04-A138)				
AR230	Liver (97-10-A074B)	Liver (97-10-A074B)				
AR231	Liver (98-09-A242A)	Liver (98-09-A242A)				
AR232	Liver Diabetic (1042)	Liver Diabetic (1042)				
AR233	Liver Diabetic (41616)	Liver Diabetic (41616)				
AR234	Liver Diabetic (41955)	Liver Diabetic (41955)				
AR235	Liver Diabetic (42352R)	Liver Diabetic (42352R)				
AR236	Liver Diabetic (42366)	Liver Diabetic (42366)				
AR237	Liver Diabetic (42483)	Liver Diabetic (42483)				
AR238	Liver Diabetic (42491)	Liver Diabetic (42491)				
AR239	Liver Diabetic (99-09-A281A)	Liver Diabetic (99-09-A281A)				
AR240	Lung	Lung				
AR241	Lung (27270)	Lung (27270)				
AR242	Lung (2727Q)	Lung (2727Q)				
AR243	Lung Cancer (4005116A1)	Lung Cancer (4005116A1)				
AR244	Lung Cancer (4005121A5)	Lung Cancer (4005121A5)				
AR245	Lung Cancer	Lung Cancer (4005121A5))				

	(4005121A5))					
AR246	Lung Cancer (4005340A4)	Lung Cancer (4005340A4)				
AR247	Mammary Gland	Mammary Gland				
AR248	Monocyte (CT)	Monocyte (CT)				
AR249	Monocyte (OCT)	Monocyte (OCT)				
AR250	Monocytes (CT)	Monocytes (CT)				
AR251	Monocytes (INFG 18 hr)	Monocytes (INFG 18 hr)				
AR252	Monocytes (INFG 18hr)	Monocytes (INFG 18hr)				
AR253	Monocytes (INFG 8-11)	Monocytes (INFG 8-11)				
AR254	Monocytes (O CT)	Monocytes (O CT)				
AR255	Muscle (91-01-A105)	Muscle (91-01-A105)				
AR256	Muscle (92-04-A059)	Muscle (92-04-A059)				
AR257	Muscle (97-11-A056d)	Muscle (97-11-A056d)				
AR258	Muscle (99-06-A210A)	Muscle (99-06-A210A)				
AR259	Muscle (99-07-A203B)	Muscle (99-07-A203B)				
AR260	Muscle (99-7-A203B)	Muscle (99-7-A203B)				
AR261	Muscle Diabetic (42352R)	Muscle Diabetic (42352R)				
AR262	Muscle Diabetic (42366)	Muscle Diabetic (42366)				
AR263	NK-19 Control	NK-19 Control				
AR264	NK-19 IL Treated 72hrs	NK-19 IL Treated 72hrs				
AR265	NK-19 UK Treated 72 hrs.	NK-19 UK Treated 72 hrs.				
AR266	Omentum Normal (94-08-B009)	Omentum Normal (94-08-B009)				
AR267	Omentum Normal (97-01-A039A)	Omentum Normal (97-01-A039A)				
AR268	Omentum Normal (97-04-A114C)	Omentum Normal (97-04-A114C)				
AR269	Omentum Normal (97-06-A117C)	Omentum Normal (97-06-A117C)				
AR270	Omentum Normal (97-09-	Omentum Normal (97-09-				

	B004C)	B004C)				
AR271	Ovarian Cancer (17717AID)	Ovarian Cancer (17717AID)				
AR272	Ovarian Cancer (9905C023RC)	Ovarian Cancer (9905C023RC)				
AR273	Ovarian Cancer (9905C032RC)	Ovarian Cancer (9905C032RC)				
AR274	Ovary (9508G045)	Ovary (9508G045)				
AR275	Ovary (9701G208)	Ovary (9701G208)				
AR276	Ovary 9806G005	Ovary 9806G005				
AR277	Pancreas	Pancreas				
AR278	Placebo	Placebo				
AR279	rIL2 Control	rIL2 Control				
AR280	RSS288L	RSS288L				
AR281	RSS288LC	RSS288LC				
AR282	Salivary Gland	Salivary Gland				
AR283	Skeletal Muscle	Skeletal Muscle				
AR284	Skeletal Muscle (91-01-A105)	Skeletal Muscle (91-01-A105)				
AR285	Skeletal Muscle (42180)	Skeletal Muscle (42180)				
AR286	Skeletal Muscle (42386)	Skeletal Muscle (42386)				
AR287	Skeletal Muscle (42461)	Skeletal Muscle (42461)				
AR288	Skeletal Muscle (91-01-A105)	Skeletal Muscle (91-01-A105)				
AR289	Skeletal Muscle (92-04-A059)	Skeletal Muscle (92-04-A059)				
AR290	Skeletal Muscle (96-08-A171)	Skeletal Muscle (96-08-A171)				
AR291	Skeletal Muscle (97-07-A190A)	Skeletal Muscle (97-07-A190A)				
AR292	Skeletal Muscle Diabetic (42352)	Skeletal Muscle Diabetic (42352)				
AR293	Skeletal Muscle Diabetic	Skeletal Muscle Diabetic				

	(42366)	(42366)				
AR294	Skeletal Muscle Diabetic (42395)	Skeletal Muscle Diabetic (42395)				
AR295	Skeletal Muscle Diabetic (42483)	Skeletal Muscle Diabetic (42483)				
AR296	Skeletal Muscle Diabetic (42491)	Skeletal Muscle Diabetic (42491)				
AR297	Skeletal Muscle Diabetic 42352	Skeletal Muscle Diabetic 42352				
AR298	Skeletal Musle (42461)	Skeletal Musle (42461)				
AR299	Small Intestine	Small Intestine				
AR300	Stomach	Stomach				
AR301	T-Cell + HDPBQ71.fc 1449 16hrs	T-Cell + HDPBQ71.fc 1449 16hrs				
AR302	T-Cell + HDPBQ71.fc 1449 6hrs	T-Cell + HDPBQ71.fc 1449 6hrs				
AR303	T-Cell + IL2 16hrs	T-Cell + IL2 16hrs				
AR304	T-Cell + IL2 6hrs	T-Cell + IL2 6hrs				
AR306	T-Cell Untreated 16hrs	T-Cell Untreated 16hrs				
AR307	T-Cell Untreated 6hrs	T-Cell Untreated 6hrs				
AR308	T-Cells 24 hours	T-Cells 24 hours				
AR309	T-Cells 24 hrs	T-Cells 24 hrs				
AR310	T-Cells 24 hrs.	T-Cells 24 hrs.				
AR311	T-Cells 24hrs	T-Cells 24hrs				
AR312	T-Cells 4 days	T-Cells 4 days				
AR313	Thymus	Thymus				
AR314	TRE	TRE				
AR315	TREC	TREC				
AR317	B lymphocyte,	B lymphocyte,				
AR318	(non-T; non-B)	(non-T; non-B)				
AR326	001 - 293 RNA (Vector Control)	001 - 293 RNA (Vector Control)				

AR327	001: Control	001: Control				
AR328	001: Control.1	001: Control.1				
AR355	Acute Lymphocyte Leukemia	Acute Lymphocyte Leukemia				
AR356	AML Patient #11	AML Patient #11				
AR357	AML Patient #2	AML Patient #2				
AR358	AML Patient #2 SGAH	AML Patient #2 SGAH				
AR359	AML Patient#2	AML Patient#2				
AR360	Aorta	Aorta				
AR361	B Cell	B Cell				
AR362	B lymphoblast	B lymphoblast				
AR363	B lymphocyte	B lymphocyte				
AR364	B lymphocytes	B lymphocytes				
AR365	B-cell	B-cell				
AR366	B-Cells	B-Cells				
AR367	B-Lymphoblast	B-Lymphoblast				
AR368	B-Lymphocytes	B-Lymphocytes				
AR369	Bladder	Bladder				
AR370	Bone Marrow	Bone Marrow				
AR371	Bronchial Epithelial Cell	Bronchial Epithelial Cell				
AR372	Bronchial Epithelial Cells	Bronchial Epithelial Cells				
AR373	Caco-2A	Caco-2A				
AR374	Caco-2B	Caco-2B				
AR375	Caco-2C	Caco-2C				
AR376	Cardiac #1	Cardiac #1				
AR377	Cardiac #2	Cardiac #2				
AR378	Chest Muscle	Chest Muscle				
AR381	Dendritic Cell	Dendritic Cell				
AR382	Dendritic cells	Dendritic cells				
AR383	E.coli	E.coli				
AR384	Epithelial Cells	Epithelial Cells				
AR385	Esophagus	Esophagus				

AR386	FPPS	FPPS				
AR387	FPPSC	FPPSC				
AR388	HepG2 Cell Line	HepG2 Cell Line				
AR389	HepG2 Cell line Buffer 1 hr.	HepG2 Cell line Buffer 1 hr.				
AR390	HepG2 Cell line Buffer 06 hr	HepG2 Cell line Buffer 06 hr				
AR391	HepG2 Cell line Buffer 24 hr.	HepG2 Cell line Buffer 24 hr.				
AR392	HepG2 Cell line Insulin 01 hr.	HepG2 Cell line Insulin 01 hr.				
AR393	HepG2 Cell line Insulin 06 hr.	HepG2 Cell line Insulin 06 hr.				
AR394	HepG2 Cell line Insulin 24 hr.	HepG2 Cell line Insulin 24 hr.				
AR398	HMC-1	HMC-1				
AR399	HMCS	HMCS				
AR400	HMSC	HMSC				
AR401	HUVEC #3	HUVEC #3				
AR402	HUVEC #4	HUVEC #4				
AR404	KIDNEY NORMAL	KIDNEY NORMAL				
AR405	KIDNEY TUMOR	KIDNEY TUMOR				
AR406	KIDNEY TUMOR					
AR407	Lymph Node	Lymph Node				
AR408	Macrophage	Macrophage				
AR409	Megakarioblast	Megakarioblast				
AR410	Monocyte	Monocyte				
AR411	Monocytes	Monocytes				
AR412	Myocardium	Myocardium				
AR413	Myocardium #3	Myocardium #3				

AR414	Myocardium #4	Myocardium #4				
AR415	Myocardium #5	Myocardium #5				
AR416	NK	NK				
AR417	NK cell	NK cell				
AR418	NK cells	NK cells				
AR419	NKYa	NKYa				
AR420	NKYa019	NKYa019				
AR421	Ovary	Ovary				
AR422	Patient #11	Patient #11				
AR423	Peripheral blood	Peripheral blood				
AR424	Primary Adipocytes	Primary Adipocytes				
AR425	Promyeloblast	Promyeloblast				
AR427	RSSWT	RSSWT				
AR428	RSSWTC	RSSWTC				
AR429	SW 480(G1)	SW 480(G1)				
AR430	SW 480(G2)	SW 480(G2)				
AR431	SW 480(G3)	SW 480(G3)				
AR432	SW 480(G4)	SW 480(G4)				
AR433	SW 480(G5)	SW 480(G5)				
AR434	T Lymphoblast	T Lymphoblast				
AR435	T Lymphocyte	T Lymphocyte				
AR436	T-Cell	T-Cell				
AR438	T-Cell,	T-Cell,				
AR439	T-Cells	T-Cells				
AR440	T-lymphoblast	T-lymphoblast				
AR441	Th 1	Th 1				
AR442	Th 2	Th 2				
AR443	Th1	Th1				
AR444	Th2	Th2				
H0004	Human Adult Spleen	Human Adult Spleen	Spleen			Uni-ZAP XR
H0007	Human Cerebellum	Human Cerebellum	Brain			Uni-ZAP XR
H0008	Whole 6 Week Old					Uni-ZAP XR

	Embryo					
H0009	Human Fetal Brain					Uni-ZAP XR
H0012	Human Fetal Kidney	Human Fetal Kidney	Kidney			Uni-ZAP XR
H0013	Human 8 Week Whole Embryo	Human 8 Week Old Embryo	Embryo			Uni-ZAP XR
H0014	Human Gall Bladder	Human Gall Bladder	Gall Bladder			Uni-ZAP XR
H0015	Human Gall Bladder, fraction II	Human Gall Bladder	Gall Bladder			Uni-ZAP XR
H0024	Human Fetal Lung III	Human Fetal Lung	Lung			Uni-ZAP XR
H0025	Human Adult Lymph Node	Human Adult Lymph Node	Lymph Node			Lambda ZAP II
H0030	Human Placenta					Uni-ZAP XR
H0031	Human Placenta	Human Placenta	Placenta			Uni-ZAP XR
H0032	Human Prostate	Human Prostate	Prostate			Uni-ZAP XR
H0033	Human Pituitary	Human Pituitary				Uni-ZAP XR
H0036	Human Adult Small Intestine	Human Adult Small Intestine	Small Int.			Uni-ZAP XR
H0038	Human Testes	Human Testes	Testis			Uni-ZAP XR
H0039	Human Pancreas Tumor	Human Pancreas Tumor	Pancreas		disease	Uni-ZAP XR
H0040	Human Testes Tumor	Human Testes Tumor	Testis		disease	Uni-ZAP XR
H0041	Human Fetal Bone	Human Fetal Bone	Bone			Uni-ZAP XR
H0042	Human Adult Pulmonary	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0046	Human Endometrial Tumor	Human Endometrial Tumor	Uterus		disease	Uni-ZAP XR
H0050	Human Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR
H0051	Human Hippocampus	Human Hippocampus	Brain			Uni-ZAP XR
H0052	Human Cerebellum	Human Cerebellum	Brain			Uni-ZAP XR
H0056	Human Umbilical Vein, Endo. remake	Human Umbilical Vein Endothelial Cells	Umbilical vein			Uni-ZAP XR
H0057	Human Fetal Spleen					Uni-ZAP XR
H0059	Human Uterine Cancer	Human Uterine Cancer	Uterus		disease	Lambda ZAP II
H0063	Human Thymus	Human Thymus	Thymus			Uni-ZAP XR

H0068	Human Skin Tumor	Human Skin Tumor	Skin		disease	Uni-ZAP XR
H0069	Human Activated T-Cells	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0071	Human Infant Adrenal Gland	Human Infant Adrenal Gland	Adrenal gland			Uni-ZAP XR
H0073	Human Leiomyeloid Carcinoma	Human Leiomyeloid Carcinoma	Muscle		disease	Uni-ZAP XR
H0077	Human Thymus Tumor	Human Thymus Tumor	Thymus		disease	Lambda ZAP II
H0081	Human Fetal Epithelium (Skin)	Human Fetal Skin	Skin			Uni-ZAP XR
H0083	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Jurkat Cells				Uni-ZAP XR
H0085	Human Colon	Human Colon				Lambda ZAP II
H0087	Human Thymus	Human Thymus				pBluescript
H0090	Human T-Cell Lymphoma	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0096	Human Parotid Cancer	Human Parotid Cancer	Parotid		disease	Lambda ZAP II
H0098	Human Adult Liver, subtracted	Human Adult Liver	Liver			Uni-ZAP XR
H0100	Human Whole Six Week Old Embryo	Human Whole Six Week Old Embryo	Embryo			Uni-ZAP XR
H0108	Human Adult Lymph Node, subtracted	Human Adult Lymph Node	Lymph Node			Uni-ZAP XR
H0111	Human Placenta, subtracted	Human Placenta	Placenta			pBluescript
H0112	Human Parathyroid Tumor, subtracted	Human Parathyroid Tumor	Parathyroid			pBluescript
H0122	Human Adult Skeletal Muscle	Human Skeletal Muscle	Sk Muscle			Uni-ZAP XR
H0123	Human Fetal Dura Mater	Human Fetal Dura Mater	Brain			Uni-ZAP XR
H0124	Human Rhabdomyosarcoma	Human Rhabdomyosarcoma	Sk Muscle		disease	Uni-ZAP XR
H0125	Cem cells cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR

H0130	LNCAP untreated	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
H0131	LNCAP + o.3nM R1881	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
H0132	LNCAP + 30nM R1881	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
H0134	Raji Cells, cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0135	Human Synovial Sarcoma	Human Synovial Sarcoma	Synovium			Uni-ZAP XR
H0136	Supt Cells, cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0139	Activated T-Cells, 4 hrs.	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0140	Activated T-Cells, 8 hrs.	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0141	Activated T-Cells, 12 hrs.	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0144	Nine Week Old Early Stage Human	9 Wk Old Early Stage Human	Embryo			Uni-ZAP XR
H0149	7 Week Old Early Stage Human, subtracted	Human Whole 7 Week Old Embryo	Embryo			Uni-ZAP XR
H0150	Human Epididymus	Epididymis	Testis			Uni-ZAP XR
H0151	Early Stage Human Liver	Human Fetal Liver	Liver			Uni-ZAP XR
H0156	Human Adrenal Gland Tumor	Human Adrenal Gland Tumor	Adrenal Gland		disease	Uni-ZAP XR
H0160	Activated T-Cells, 12 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0161	Activated T-Cells, 24 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0163	Human Synovium	Human Synovium	Synovium			Uni-ZAP XR
H0165	Human Prostate Cancer, Stage B2	Human Prostate Cancer, stage B2	Prostate		disease	Uni-ZAP XR
H0166	Human Prostate Cancer, Stage B2 fraction	Human Prostate Cancer, stage B2	Prostate		disease	Uni-ZAP XR
H0169	Human Prostate Cancer, Stage C fraction	Human Prostate Cancer, stage C	Prostate		disease	Uni-ZAP XR
H0170	12 Week Old Early Stage Human	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0171	12 Week Old Early Stage	Twelve Week Old Early Stage	Embryo			Uni-ZAP XR

	Human, II	Human				
H0172	Human Fetal Brain, random primed	Human Fetal Brain	Brain			Lambda ZAP II
H0176	CAMA1Ee Cell Line	CAMA1Ee Cell Line	Breast	Cell Line		Uni-ZAP XR
H0178	Human Fetal Brain	Human Fetal Brain	Brain			Uni-ZAP XR
H0179	Human Neutrophil	Human Neutrophil	Blood	Cell Line		Uni-ZAP XR
H0181	Human Primary Breast Cancer	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0182	Human Primary Breast Cancer	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0187	Resting T-Cell	T-Cells	Blood	Cell Line		Lambda ZAP II
H0188	Human Normal Breast	Human Normal Breast	Breast			Uni-ZAP XR
H0192	Cem Cells, cyclohexamide treated, subtra	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0194	Human Cerebellum, subtracted	Human Cerebellum	Brain			pBluescript
H0196	Human Cardiomyopathy, subtracted	Human Cardiomyopathy	Heart			Uni-ZAP XR
H0204	Human Colon Cancer, subtracted	Human Colon Cancer	Colon			pBluescript
H0208	Early Stage Human Lung, subtracted	Human Fetal Lung	Lung			pBluescript
H0211	Human Prostate,differential expression	Human Prostate	Prostate			pBluescript
H0212	Human Prostate, subtracted	Human Prostate	Prostate			pBluescript
H0213	Human Pituitary, subtracted	Human Pituitary				Uni-ZAP XR
H0214	Raji cells, cyclohexamide treated, subtracted	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		pBluescript
H0218	Activated T-Cells, 0hrs,	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR

	subtracted					
H0222	Activated T-Cells, 8 hrs, subtracted	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0224	Activated T-Cells, 12 hrs, subtracted	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0225	Activated T-Cells, 12hrs, differentially expressed	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0231	Human Colon, subtraction	Human Colon				pBluescript
H0233	Human Fetal Heart, Differential (Adult-Specific)	Human Fetal Heart	Heart			pBluescript
H0235	Human colon cancer, metaticized to liver, subtraction	Human Colon Cancer, metasticized to liver	Liver			pBluescript
H0239	Human Kidney Tumor	Human Kidney Tumor	Kidney		disease	Uni-ZAP XR
H0242	Human Fetal Heart, Differential (Fetal-Specific)	Human Fetal Heart	Heart			pBluescript
H0244	Human 8 Week Whole Embryo, subtracted	Human 8 Week Old Embryo	Embryo			Uni-ZAP XR
H0250	Human Activated Monocytes	Human Monocytes				Uni-ZAP XR
H0251	Human Chondrosarcoma	Human Chondrosarcoma	Cartilage		disease	Uni-ZAP XR
H0252	Human Osteosarcoma	Human Osteosarcoma	Bone		disease	Uni-ZAP XR
H0253	Human adult testis, large inserts	Human Adult Testis	Testis			Uni-ZAP XR
H0254	Breast Lymph node cDNA library	Breast Lymph Node	Lymph Node			Uni-ZAP XR
H0255	breast lymph node CDNA library	Breast Lymph Node	Lymph Node			Lambda ZAP II
H0261	H. cerebellum, Enzyme subtracted	Human Cerebellum	Brain			Uni-ZAP XR
H0263	human colon cancer	Human Colon Cancer	Colon		disease	Lambda ZAP II

H0264	human tonsils	Human Tonsil	Tonsil			Uni-ZAP XR
H0265	Activated T-Cell (12hs)/Thiouridine labelledEco	T-Cells	Blood	Cell Line		Uni-ZAP XR
H0266	Human Microvascular Endothelial Cells, fract. A	HMEC	Vein	Cell Line		Lambda ZAP II
H0267	Human Microvascular Endothelial Cells, fract. B	HMEC	Vein	Cell Line		Lambda ZAP II
H0268	Human Umbilical Vein Endothelial Cells, fract. A	HUVE Cells	Umbilical vein	Cell Line		Lambda ZAP II
H0270	HPAS (human pancreas, subtracted)	Human Pancreas	Pancreas			Uni-ZAP XR
H0271	Human Neutrophil, Activated	Human Neutrophil - Activated	Blood	Cell Line		Uni-ZAP XR
H0272	HUMAN TONSILS, FRACTION 2	Human Tonsil	Tonsil			Uni-ZAP XR
H0275	Human Infant Adrenal Gland, Subtracted	Human Infant Adrenal Gland	Adrenal gland			pBluescript
H0280	K562 + PMA (36 hrs)	K562 Cell line	cell line	Cell Line		ZAP Express
H0284	Human OB MG63 control fraction I	Human Osteoblastoma MG63 cell line	Bone	Cell Line		Uni-ZAP XR
H0286	Human OB MG63 treated (10 nM E2) fraction I	Human Osteoblastoma MG63 cell line	Bone	Cell Line		Uni-ZAP XR
H0288	Human OB HOS control fraction I	Human Osteoblastoma HOS cell line	Bone	Cell Line		Uni-ZAP XR
H0290	Human OB HOS treated (1 nM E2) fraction I	Human Osteoblastoma HOS cell line	Bone	Cell Line		Uni-ZAP XR
H0292	Human OB HOS treated (10 nM E2) fraction I	Human Osteoblastoma HOS cell line	Bone	Cell Line		Uni-ZAP XR
H0294	Amniotic Cells - TNF induced	Amniotic Cells - TNF induced	Placenta	Cell Line		Uni-ZAP XR
H0295	Amniotic Cells - Primary Culture	Amniotic Cells - Primary Culture	Placenta	Cell Line		Uni-ZAP XR

H0298	HCBB"s differential consolidation	CAMA1Ee Cell Line	Breast	Cell Line		Uni-ZAP XR
H0305	CD34 positive cells (Cord Blood)	CD34 Positive Cells	Cord Blood			ZAP Express
H0306	CD34 depleted Buffy Coat (Cord Blood)	CD34 Depleted Buffy Coat (Cord Blood)	Cord Blood			ZAP Express
H0309	Human Chronic Synovitis	Synovium, Chronic Synovitis/ Osteoarthritis	Synovium		disease	Uni-ZAP XR
H0310	human caudate nucleus	Brain	Brain			Uni-ZAP XR
H0313	human pleural cancer	pleural cancer			disease	pBluescript
H0316	HUMAN STOMACH	Human Stomach	Stomach			Uni-ZAP XR
H0318	HUMAN B CELL LYMPHOMA	Human B Cell Lymphoma	Lymph Node		disease	Uni-ZAP XR
H0320	Human frontal cortex	Human Frontal Cortex	Brain			Uni-ZAP XR
H0327	human corpus colosum	Human Corpus Callosum	Brain			Uni-ZAP XR
H0328	human ovarian cancer	Ovarian Cancer	Ovary		disease	Uni-ZAP XR
H0329	Dermatofibrosarcoma Protuberance	Dermatofibrosarcoma Protuberans	Skin		disease	Uni-ZAP XR
H0331	Hepatocellular Tumor	Hepatocellular Tumor	Liver		disease	Lambda ZAP II
H0333	Hemangiopericytoma	Hemangiopericytoma	Blood vessel		disease	Lambda ZAP II
H0334	Kidney cancer	Kidney Cancer	Kidney		disease	Uni-ZAP XR
H0341	Bone Marrow Cell Line (RS4;11)	Bone Marrow Cell Line RS4;11	Bone Marrow	Cell Line		Uni-ZAP XR
H0343	stomach cancer (human)	Stomach Cancer - 5383A (human)			disease	Uni-ZAP XR
H0346	Brain-medulloblastoma	Brain (Medulloblastoma)-9405C006R	Brain		disease	Uni-ZAP XR
H0350	Human Fetal Liver, mixed 10 & 14 week	Human Fetal Liver, mixed 10&14 Week	Liver			Uni-ZAP XR
H0351	Glioblastoma	Glioblastoma	Brain		disease	Uni-ZAP XR
H0352	wilm"s tumor	Wilm"s Tumor			disease	Uni-ZAP XR
H0354	Human Leukocytes	Human Leukocytes	Blood	Cell Line		pCMVSport 1
H0355	Human Liver	Human Liver, normal Adult				pCMVSport 1

H0356	Human Kidney	Human Kidney	Kidney			pCMVSport 1
H0357	H. Normalized Fetal Liver, II	Human Fetal Liver	Liver			Uni-ZAP XR
H0359	KMH2 cell line	KMH2				ZAP Express
H0369	H. Atrophic Endometrium	Atrophic Endometrium and myometrium				Uni-ZAP XR
H0370	H. Lymph node breast Cancer	Lymph node with Met. Breast Cancer			disease	Uni-ZAP XR
H0373	Human Heart	Human Adult Heart	Heart			pCMVSport 1
H0375	Human Lung	Human Lung				pCMVSport 1
H0380	Human Tongue, frac 2	Human Tongue				pSport1
H0381	Bone Cancer	Bone Cancer			disease	Uni-ZAP XR
H0383	Human Prostate BPH, re-excision	Human Prostate BPH				Uni-ZAP XR
H0384	Brain, Kozak	Human Brain				pCMVSport 1
H0386	Leukocyte and Lung; 4 screens	Human Leukocytes	Blood	Cell Line		pCMVSport 1
H0390	Human Amygdala Depression, re-excision	Human Amygdala Depression			disease	pBluescript
H0392	H. Meningima, M1	Human Meningima	brain			pSport1
H0393	Fetal Liver, subtraction II	Human Fetal Liver	Liver			pBluescript
H0394	A-14 cell line	Redd-Sternberg cell				ZAP Express
H0399	Human Kidney Cortex, re-rescue	Human Kidney Cortex				Lambda ZAP II
H0402	CD34 depleted Buffy Coat (Cord Blood), re-excision	CD34 Depleted Buffy Coat (Cord Blood)	Cord Blood			ZAP Express
H0404	H. Umbilical Vein endothelial cells, uninduced	HUVE Cells	Umbilical vein	Cell Line		Uni-ZAP XR
H0405	Human Pituitary, subtracted VI	Human Pituitary				pBluescript
H0406	H Amygdala Depression,	Human Amygdala Depression				Uni-ZAP XR

	subtracted					
H0408	Human kidney Cortex, subtracted	Human Kidney Cortex				pBluescript
H0409	H. Striatum Depression, subtracted	Human Brain, Striatum Depression	Brain			pBluescript
H0410	H. Male bladder, adult	H Male Bladder, Adult	Bladder			pSport1
H0411	H Female Bladder, Adult	Human Female Adult Bladder	Bladder			pSport1
H0412	Human umbilical vein endothelial cells, IL-4 induced	HUVE Cells	Umbilical vein	Cell Line		pSport1
H0413	Human Umbilical Vein Endothelial Cells, uninduced	HUVE Cells	Umbilical vein	Cell Line		pSport1
H0415	H. Ovarian Tumor, II, OV5232	Ovarian Tumor, OV5232	Ovary		disease	pCMVSport 2.0
H0416	Human Neutrophils, Activated, re-excision	Human Neutrophil - Activated	Blood	Cell Line		pBluescript
H0417	Human Pituitary, subtracted VIII	Human Pituitary				pBluescript
H0418	Human Pituitary, subtracted VII	Human Pituitary				pBluescript
H0421	Human Bone Marrow, re-excision	Bone Marrow				pBluescript
H0422	T-Cell PHA 16 hrs	T-Cells	Blood	Cell Line		pSport1
H0423	T-Cell PHA 24 hrs	T-Cells	Blood	Cell Line		pSport1
H0424	Human Pituitary, subt IX	Human Pituitary				pBluescript
H0427	Human Adipose	Human Adipose, left hiplipoma				pSport1
H0428	Human Ovary	Human Ovary Tumor	Ovary			pSport1
H0429	K562 + PMA (36 hrs),re-excision	K562 Cell line	cell line	Cell Line		ZAP Express
H0431	H. Kidney Medulla, re-excision	Kidney medulla	Kidney			pBluescript
H0433	Human Umbilical Vein	HUVE Cells	Umbilical vein	Cell Line		pBluescript

	Endothelial cells, frac B, re-excision					
H0435	Ovarian Tumor 10-3-95	Ovarian Tumor, OV350721	Ovary			pCMVSport 2.0
H0436	Resting T-Cell Library,II	T-Cells	Blood	Cell Line		pSport1
H0438	H. Whole Brain #2, re-excision	Human Whole Brain #2				ZAP Express
H0441	H. Kidney Cortex, subtracted	Kidney cortex	Kidney			pBluescript
H0444	Spleen metastic melanoma	Spleen, Metastic malignant melanoma	Spleen		disease	pSport1
H0445	Spleen, Chronic lymphocytic leukemia	Human Spleen, CLL	Spleen		disease	pSport1
H0455	H. Striatum Depression, subt	Human Brain, Striatum Depression	Brain			pBluescript
H0457	Human Eosinophils	Human Eosinophils				pSport1
H0458	CD34+ cell, I, frac II	CD34 positive cells				pSport1
H0459	CD34+cells, II, FRACTION 2	CD34 positive cells				pCMVSport 2.0
H0461	H. Kidney Medulla, subtracted	Kidney medulla	Kidney			pBluescript
H0478	Salivary Gland, Lib 2	Human Salivary Gland	Salivary gland			pSport1
H0483	Breast Cancer cell line, MDA 36	Breast Cancer Cell line, MDA 36				pSport1
H0484	Breast Cancer Cell line, angiogenic	Breast Cancer Cell line, Angiogenic, 36T3				pSport1
H0485	Hodgkin''s Lymphoma I	Hodgkin''s Lymphoma I			disease	pCMVSport 2.0
H0486	Hodgkin''s Lymphoma II	Hodgkin''s Lymphoma II			disease	pCMVSport 2.0
H0488	Human Tonsils, Lib 2	Human Tonsils				pCMVSport 2.0
H0492	HL-60, RA 4h, Subtracted	HL-60 Cells, RA stimulated for 4H	Blood	Cell Line		Uni-ZAP XR
H0494	Keratinocyte	Keratinocyte				pCMVSport 2.0
H0497	HEL cell line	HEL cell line		HEL 92.1.7		pSport1
H0505	Human Astrocyte	Human Astrocyte				pSport1

H0506	Ulcerative Colitis	Colon	Colon			pSport1
H0509	Liver, Hepatoma	Human Liver, Hepatoma, patient 8	Liver		disease	pCMVSport 3.0
H0510	Human Liver, normal	Human Liver, normal, Patient # 8	Liver			pCMVSport 3.0
H0518	pBMC stimulated w/ poly I/C	pBMC stimulated with poly I/C				pCMVSport 3.0
H0519	NTERA2, control	NTERA2, Teratocarcinoma cell line				pCMVSport 3.0
H0520	NTERA2 + retinoic acid, 14 days	NTERA2, Teratocarcinoma cell line				pSport1
H0521	Primary Dendritic Cells, lib 1	Primary Dendritic cells				pCMVSport 3.0
H0522	Primary Dendritic cells,frac 2	Primary Dendritic cells				pCMVSport 3.0
H0525	PCR, pBMC I/C treated	pBMC stimulated with poly I/C				PCRII
H0529	Myoloid Progenitor Cell Line	TF-1 Cell Line; Myoloid progenitor cell line				pCMVSport 3.0
H0530	Human Dermal Endothelial Cells,untreated	Human Dermal Endothelial Cells; untreated				pSport1
H0537	H. Primary Dendritic Cells,lib 3	Primary Dendritic cells				pCMVSport 2.0
H0538	Merkel Cells	Merkel cells	Lymph node			pSport1
H0539	Pancreas Islet Cell Tumor	Pancreas Islet Cell Tumour	Pancreas		disease	pSport1
H0542	T Cell helper I	Helper T cell				pCMVSport 3.0
H0543	T cell helper II	Helper T cell				pCMVSport 3.0
H0544	Human endometrial stromal cells	Human endometrial stromal cells				pCMVSport 3.0
H0545	Human endometrial stromal cells-treated with progesterone	Human endometrial stromal cells-treated with proge				pCMVSport 3.0
H0546	Human endometrial	Human endometrial stromal				pCMVSport 3.0

	stromal cells-treated with estradiol	cells-treated with estra				
H0547	NTERA2 teratocarcinoma cell line+retinoic acid (14 days)	NTERA2, Teratocarcinoma cell line				pSport1
H0549	H. Epididiymus, caput & corpus	Human Epididiymus, caput and corpus				Uni-ZAP XR
H0550	H. Epididiymus, cauda	Human Epididiymus, cauda				Uni-ZAP XR
H0551	Human Thymus Stromal Cells	Human Thymus Stromal Cells				pCMVSport 3.0
H0553	Human Placenta	Human Placenta				pCMVSport 3.0
H0555	Rejected Kidney, lib 4	Human Rejected Kidney	Kidney		disease	pCMVSport 3.0
H0556	Activated T-cell(12h)/Thiouridine-re-excision	T-Cells	Blood	Cell Line		Uni-ZAP XR
H0559	HL-60, PMA 4H, re-excision	HL-60 Cells, PMA stimulated 4H	Blood	Cell Line		Uni-ZAP XR
H0560	KMH2	KMH2				pCMVSport 3.0
H0561	L428	L428				pCMVSport 3.0
H0563	Human Fetal Brain, normalized 50021F	Human Fetal Brain				pCMVSport 2.0
H0564	Human Fetal Brain, normalized C5001F	Human Fetal Brain				pCMVSport 2.0
H0566	Human Fetal Brain,normalized c50F	Human Fetal Brain				pCMVSport 2.0
H0567	Human Fetal Brain, normalized A5002F	Human Fetal Brain				pCMVSport 2.0
H0569	Human Fetal Brain, normalized CO	Human Fetal Brain				pCMVSport 2.0
H0570	Human Fetal Brain, normalized C500H	Human Fetal Brain				pCMVSport 2.0
H0571	Human Fetal Brain, normalized C500HE	Human Fetal Brain				pCMVSport 2.0

H0572	Human Fetal Brain, normalized AC5002	Human Fetal Brain				pCMVSport 2.0
H0574	Hepatocellular Tumor; re-excision	Hepatocellular Tumor	Liver		disease	Lambda ZAP II
H0575	Human Adult Pulmonary;re-excision	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0576	Resting T-Cell; re-excision	T-Cells	Blood	Cell Line		Lambda ZAP II
H0578	Human Fetal Thymus	Fetal Thymus	Thymus			pSport1
H0580	Dendritic cells, pooled	Pooled dendritic cells				pCMVSport 3.0
H0581	Human Bone Marrow, treated	Human Bone Marrow	Bone Marrow			pCMVSport 3.0
H0583	B Cell lymphoma	B Cell Lymphoma	B Cell		disease	pCMVSport 3.0
H0585	Activated T-Cells,12 hrs,re-excision	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0586	Healing groin wound, 6.5 hours post incision	healing groin wound, 6.5 hours post incision - 2/	groin		disease	pCMVSport 3.0
H0587	Healing groin wound; 7.5 hours post incision	Groin-2/19/97	groin		disease	pCMVSport 3.0
H0589	CD34 positive cells (cord blood),re-ex	CD34 Positive Cells	Cord Blood			ZAP Express
H0590	Human adult small intestine,re-excision	Human Adult Small Intestine	Small Int.			Uni-ZAP XR
H0591	Human T-cell lymphoma;re-excision	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0592	Healing groin wound - zero hr post-incision (control)	HGS wound healing project; abdomen			disease	pCMVSport 3.0
H0593	Olfactory epithelium;nasalcavity	Olfactory epithelium from roof of left nasal cacit				pCMVSport 3.0
H0594	Human Lung Cancer;re-excision	Human Lung Cancer	Lung		disease	Lambda ZAP II
H0595	Stomach cancer	Stomach Cancer - 5383A			disease	Uni-ZAP XR

	(human);re-excision	(human)				
H0596	Human Colon Cancer;re-excision	Human Colon Cancer	Colon			Lambda ZAP II
H0597	Human Colon; re-excision	Human Colon				Lambda ZAP II
H0598	Human Stomach;re-excision	Human Stomach	Stomach			Uni-ZAP XR
H0599	Human Adult Heart;re-excision	Human Adult Heart	Heart			Uni-ZAP XR
H0600	Healing Abdomen wound;70&90 min post incision	Abdomen			disease	pCMVSport 3.0
H0601	Healing Abdomen Wound;15 days post incision	Abdomen			disease	pCMVSport 3.0
H0602	Healing Abdomen Wound;21&29 days post incision	Abdomen			disease	pCMVSport 3.0
H0604	Human Pituitary, re-excision	Human Pituitary				pBluescript
H0606	Human Primary Breast Cancer;re-excision	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0613	H.Leukocytes, normalized cot 5B	H.Leukocytes				pCMVSport 1
H0614	H. Leukocytes, normalized cot 500 A	H.Leukocytes				pCMVSport 1
H0615	Human Ovarian Cancer Reexcision	Ovarian Cancer	Ovary		disease	Uni-ZAP XR
H0616	Human Testes, Reexcision	Human Testes	Testis			Uni-ZAP XR
H0617	Human Primary Breast Cancer Reexcision	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0618	Human Adult Testes, Large Inserts, Reexcision	Human Adult Testis	Testis			Uni-ZAP XR
H0619	Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR

H0620	Human Fetal Kidney; Reexcision	Human Fetal Kidney	Kidney			Uni-ZAP XR
H0622	Human Pancreas Tumor; Reexcision	Human Pancreas Tumor	Pancreas		disease	Uni-ZAP XR
H0623	Human Umbilical Vein; Reexcision	Human Umbilical Vein Endothelial Cells	Umbilical vein			Uni-ZAP XR
H0624	12 Week Early Stage Human II; Reexcision	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0625	Ku 812F Basophils Line	Ku 812F Basophils				pSport1
H0626	Saos2 Cells; Untreated	Saos2 Cell Line; Untreated				pSport1
H0627	Saos2 Cells; Vitamin D3 Treated	Saos2 Cell Line; Vitamin D3 Treated				pSport1
H0628	Human Pre-Differentiated Adipocytes	Human Pre-Differentiated Adipocytes				Uni-ZAP XR
H0631	Saos2, Dexamethosome Treated	Saos2 Cell Line; Dexamethosome Treated				pSport1
H0632	Hepatocellular Tumor;re-excision	Hepatocellular Tumor	Liver			Lambda ZAP II
H0633	Lung Carcinoma A549 TNFalpha activated	TNFalpha activated A549--Lung Carcinoma			disease	pSport1
H0634	Human Testes Tumor, re-excision	Human Testes Tumor	Testis		disease	Uni-ZAP XR
H0635	Human Activated T-Cells, re-excision	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0637	Dendritic Cells From CD34 Cells	Dentritic cells from CD34 cells				pSport1
H0638	CD40 activated monocyte dendridic cells	CD40 activated monocyte dendridic cells				pSport1
H0640	Ficolled Human Stromal Cells, Untreated	Ficolled Human Stromal Cells, Untreated				Other
H0641	LPS activated derived dendritic cells	LPS activated monocyte derived dendritic cells				pSport1
H0642	Hep G2 Cells, lambda	Hep G2 Cells				Other

	library					
H0643	Hep G2 Cells, PCR library	Hep G2 Cells				Other
H0644	Human Placenta (re-excision)	Human Placenta	Placenta			Uni-ZAP XR
H0645	Fetal Heart, re-excision	Human Fetal Heart	Heart			Uni-ZAP XR
H0646	Lung, Cancer (4005313 A3): Invasive Poorly Differentiated Lung Adenocarcinoma,	Metastatic squamous cell lung carcinoma, poorly di				pSport1
H0647	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic	Invasive poorly differentiated lung adenocarcinoma			disease	pSport1
H0648	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot	Papillary Cstic neoplasm of low malignant potentia			disease	pSport1
H0649	Lung, Normal: (4005313 B1)	Normal Lung				pSport1
H0650	B-Cells	B-Cells				pCMVSport 3.0
H0651	Ovary, Normal: (9805C040R)	Normal Ovary				pSport1
H0652	Lung, Normal: (4005313 B1)	Normal Lung				pSport1
H0653	Stromal Cells	Stromal Cells				pSport1
H0656	B-cells (unstimulated)	B-cells (unstimulated)				pSport1
H0657	B-cells (stimulated)	B-cells (stimulated)				pSport1
H0658	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	9809C332- Poorly differentiate	Ovary & Fallopian Tubes		disease	pSport1
H0659	Ovary, Cancer	Grade II Papillary Carcinoma,	Ovary		disease	pSport1

	(15395A1F): Grade II Papillary Carcinoma	Ovary				
H0660	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	Poorly differentiated carcinoma, ovary			disease	pSport1
H0661	Breast, Cancer: (4004943 A5)	Breast cancer			disease	pSport1
H0662	Breast, Normal: (4005522B2)	Normal Breast - #4005522(B2)	Breast			pSport1
H0663	Breast, Cancer: (4005522 A2)	Breast Cancer - #4005522(A2)	Breast		disease	pSport1
H0664	Breast, Cancer: (9806C012R)	Breast Cancer	Breast		disease	pSport1
H0665	Stromal cells 3.88	Stromal cells 3.88				pSport1
H0666	Ovary, Cancer: (4004332 A2)	Ovarian Cancer, Sample #4004332A2			disease	pSport1
H0667	Stromal cells(HBM3.18)	Stromal cell(HBM 3.18)				pSport1
H0668	stromal cell clone 2.5	stromal cell clone 2.5				pSport1
H0670	Ovary, Cancer(4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	Ovarian Cancer - 4004650A3				pSport1
H0672	Ovary, Cancer: (4004576 A8)	Ovarian Cancer(4004576A8)	Ovary			pSport1
H0673	Human Prostate Cancer, Stage B2; re-excision	Human Prostate Cancer, stage B2	Prostate			Uni-ZAP XR
H0674	Human Prostate Cancer, Stage C; re-excission	Human Prostate Cancer, stage C	Prostate			Uni-ZAP XR
H0675	Colon, Cancer: (9808C064R)	Colon Cancer 9808C064R				pCMVSport 3.0
H0677	TNFR degenerate oligo	B-Cells				PCRII
H0678	screened clones from placental library	Placenta	Placenta			Other

H0682	Serous Papillary Adenocarcinoma	serous papillary adenocarcinoma (9606G304SPA3B)				pCMVSport 3.0
H0683	Ovarian Serous Papillary Adenocarcinoma	Serous papillary adenocarcinoma, stage 3C (9804G01				pCMVSport 3.0
H0684	Serous Papillary Adenocarcinoma	Ovarian Cancer-9810G606	Ovaries			pCMVSport 3.0
H0685	Adenocarcinoma of Ovary, Human Cell Line, # OVCAR-3	Adenocarcinoma of Ovary, Human Cell Line, # OVCAR-				pCMVSport 3.0
H0686	Adenocarcinoma of Ovary, Human Cell Line	Adenocarcinoma of Ovary, Human Cell Line, # SW-626				pCMVSport 3.0
H0687	Human normal ovary(#9610G215)	Human normal ovary(#9610G215)	Ovary			pCMVSport 3.0
H0688	Human Ovarian Cancer(#9807G017)	Human Ovarian cancer(#9807G017),mRNA from Maura Ru				pCMVSport 3.0
H0689	Ovarian Cancer	Ovarian Cancer, #9806G019				pCMVSport 3.0
H0690	Ovarian Cancer, # 9702G001	Ovarian Cancer, #9702G001				pCMVSport 3.0
H0691	Normal Ovary, #9710G208	normal ovary, #9710G208				pCMVSport 3.0
H0693	Normal Prostate #ODQ3958EN	Normal Prostate Tissue # ODQ3958EN				pCMVSport 3.0
H0694	Prostate gland adenocarcinoma	Prostate gland, adenocarcinoma, mod/diff, gleason	prostate gland			pCMVSport 3.0
H0695	mononucleocytes from patient	mononucleocytes from patient at Shady Grove Hospit				pCMVSport 3.0
N0009	Human Hippocampus, prescreened	Human Hippocampus				
S0001	Brain frontal cortex	Brain frontal cortex	Brain			Lambda ZAP II

S0002	Monocyte activated	Monocyte-activated	blood	Cell Line		Uni-ZAP XR
S0003	Human Osteoclastoma	Osteoclastoma	bone		disease	Uni-ZAP XR
S0004	Prostate	Prostate BPH	Prostate			Lambda ZAP II
S0006	Neuroblastoma	Human Neural Blastoma			disease	pCDNA
S0007	Early Stage Human Brain	Human Fetal Brain				Uni-ZAP XR
S0010	Human Amygdala	Amygdala				Uni-ZAP XR
S0011	STROMAL - OSTEOCLASTOMA	Osteoclastoma	bone		disease	Uni-ZAP XR
S0013	Prostate	Prostate	prostate			Uni-ZAP XR
S0014	Kidney Cortex	Kidney cortex	Kidney			Uni-ZAP XR
S0015	Kidney medulla	Kidney medulla	Kidney			Uni-ZAP XR
S0016	Kidney Pyramids	Kidney pyramids	Kidney			Uni-ZAP XR
S0022	Human Osteoclastoma Stromal Cells - unamplified	Osteoclastoma Stromal Cells				Uni-ZAP XR
S0024	Human Kidney Medulla - unamplified	Human Kidney Medulla				
S0026	Stromal cell TF274	stromal cell	Bone marrow	Cell Line		Uni-ZAP XR
S0027	Smooth muscle, serum treated	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0028	Smooth muscle,control	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0029	brain stem	Brain stem	brain			Uni-ZAP XR
S0031	Spinal cord	Spinal cord	spinal cord			Uni-ZAP XR
S0032	Smooth muscle-ILb induced	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0036	Human Substantia Nigra	Human Substantia Nigra				Uni-ZAP XR
S0037	Smooth muscle, IL1b induced	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0038	Human Whole Brain #2 - Oligo dT > 1.5Kb	Human Whole Brain #2				ZAP Express
S0039	Hypothalamus	Hypothalamus	Brain			Uni-ZAP XR
S0040	Adipocytes	Human Adipocytes from Osteoclastoma				Uni-ZAP XR

S0044	Prostate BPH	prostate BPH	Prostate		disease	Uni-ZAP XR
S0045	Endothelial cells-control	Endothelial cell	endothelial cell-lung	Cell Line		Uni-ZAP XR
S0046	Endothelial-induced	Endothelial cell	endothelial cell-lung	Cell Line		Uni-ZAP XR
S0048	Human Hypothalamus, Alzheimer"s	Human Hypothalamus, Alzheimer"s			disease	Uni-ZAP XR
S0049	Human Brain, Striatum	Human Brain, Striatum				Uni-ZAP XR
S0050	Human Frontal Cortex, Schizophrenia	Human Frontal Cortex, Schizophrenia			disease	Uni-ZAP XR
S0051	Human Hypothalmus,Schizophrenia	Human Hypothalamus, Schizophrenia			disease	Uni-ZAP XR
S0052	neutrophils control	human neutrophils	blood	Cell Line		Uni-ZAP XR
S0053	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0106	STRIATUM DEPRESSION		BRAIN		disease	Uni-ZAP XR
S0110	Brain Amygdala Depression		Brain		disease	Uni-ZAP XR
S0112	Hypothalamus		Brain			Uni-ZAP XR
S0114	Anergic T-cell	Anergic T-cell		Cell Line		Uni-ZAP XR
S0116	Bone marrow	Bone marrow	Bone marrow			Uni-ZAP XR
S0124	Smooth muscle-edited A	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0126	Osteoblasts	Osteoblasts	Knee	Cell Line		Uni-ZAP XR
S0132	Epithelial-TNFa and INF induced	Airway Epithelial				Uni-ZAP XR
S0134	Apoptotic T-cell	apoptotic cells		Cell Line		Uni-ZAP XR
S0136	PERM TF274	stromal cell	Bone marrow	Cell Line		Lambda ZAP II
S0140	eosinophil-IL5 induced	eosinophil	lung	Cell Line		Uni-ZAP XR
S0142	Macrophage-oxLDL	macrophage-oxidized LDL treated	blood	Cell Line		Uni-ZAP XR
S0144	Macrophage (GM-CSF	Macrophage (GM-CSF treated)				Uni-ZAP XR

	treated)					
S0146	prostate-edited	prostate BPH	Prostate			Uni-ZAP XR
S0148	Normal Prostate	Prostate	prostate			Uni-ZAP XR
S0150	LNCAP prostate cell line	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
S0152	PC3 Prostate cell line	PC3 prostate cell line				Uni-ZAP XR
S0190	Prostate BPH,Lib 2, subtracted	Human Prostate BPH				pSport1
S0192	Synovial Fibroblasts (control)	Synovial Fibroblasts				pSport1
S0194	Synovial hypoxia	Synovial Fibroblasts				pSport1
S0196	Synovial IL-1/TNF stimulated	Synovial Fibroblasts				pSport1
S0206	Smooth Muscle- HASTE normalized	Smooth muscle	Pulmanary artery	Cell Line		pBluescript
S0210	Messangial cell, frac 2	Messangial cell				pSport1
S0212	Bone Marrow Stromal Cell, untreated	Bone Marrow Stromal Cell,untreated				pSport1
S0214	Human Osteoclastoma, re-excision	Osteoclastoma	bone		disease	Uni-ZAP XR
S0216	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0218	Apoptotic T-cell, re-excision	apoptotic cells		Cell Line		Uni-ZAP XR
S0220	H. hypothalamus, frac A;re-excision	Hypothalamus	Brain			ZAP Express
S0222	H. Frontal cortex,epileptic;re-excision	H. Brain, Frontal Cortex, Epileptic	Brain		disease	Uni-ZAP XR
S0242	Synovial Fibroblasts (Il1/TNF), subt	Synovial Fibroblasts				pSport1
S0250	Human Osteoblasts II	Human Osteoblasts	Femur		disease	pCMVSport 2.0
S0260	Spinal Cord, re-excision	Spinal cord	spinal cord			Uni-ZAP XR
S0276	Synovial hypoxia-RSF	Synovial fobroblasts	Synovial tissue			pSport1

	subtracted	(rheumatoid)				
S0278	H Macrophage (GM-CSF treated), re-excision	Macrophage (GM-CSF treated)				Uni-ZAP XR
S0280	Human Adipose Tissue, re-excision	Human Adipose Tissue				Uni-ZAP XR
S0282	Brain Frontal Cortex, re-excision	Brain frontal cortex	Brain			Lambda ZAP II
S0294	Larynx tumor	Larynx tumor	Larynx,vocal cord		disease	pSport1
S0298	Bone marrow stroma,treated	Bone marrow stroma,treatedSB	Bone marrow			pSport1
S0300	Frontal lobe,dementia;re-excision	Frontal Lobe dementia/Alzheimer"s	Brain			Uni-ZAP XR
S0312	Human osteoarthritic;fraction II	Human osteoarthritic cartilage			disease	pSport1
S0314	Human osteoarthritis;fraction I	Human osteoarthritic cartilage			disease	pSport1
S0328	Palate carcinoma	Palate carcinoma	Uvula		disease	pSport1
S0330	Palate normal	Palate normal	Uvula			pSport1
S0332	Pharynx carcinoma	Pharynx carcinoma	Hypopharynx			pSport1
S0334	Human Normal Cartilage Fraction III	Human Normal Cartilage				pSport1
S0336	Human Normal Cartilage Fraction IV	Human Normal Cartilage				pSport1
S0338	Human Osteoarthritic Cartilage Fraction III	Human osteoarthritic cartilage			disease	pSport1
S0342	Adipocytes;re-excision	Human Adipocytes from Osteoclastoma				Uni-ZAP XR
S0344	Macrophage-oxLDL; re-excision	macrophage-oxidized LDL treated	blood	Cell Line		Uni-ZAP XR
S0346	Human Amygdala;re-excision	Amygdala				Uni-ZAP XR
S0350	Pharynx Carcinoma	Pharynx carcinoma	Hypopharynx		disease	pSport1

S0354	Colon Normal II	Colon Normal	Colon			pSport1
S0356	Colon Carcinoma	Colon Carcinoma	Colon		disease	pSport1
S0358	Colon Normal III	Colon Normal	Colon			pSport1
S0360	Colon Tumor II	Colon Tumor	Colon		disease	pSport1
S0364	Human Quadriceps	Quadriceps muscle				pSport1
S0366	Human Soleus	Soleus Muscle				pSport1
S0368	Human Pancreatic Langerhans	Islets of Langerhans				pSport1
S0372	Larynx carcinoma III	Larynx carcinoma			disease	pSport1
S0374	Normal colon	Normal colon				pSport1
S0376	Colon Tumor	Colon Tumor			disease	pSport1
S0378	Pancreas normal PCA4 No	Pancreas Normal PCA4 No				pSport1
S0380	Pancreas Tumor PCA4 Tu	Pancreas Tumor PCA4 Tu			disease	pSport1
S0386	Human Whole Brain, re-excision	Whole brain	Brain			ZAP Express
S0388	Human Hypothalamus,schizophrenia, re-excision	Human Hypothalamus, Schizophrenia			disease	Uni-ZAP XR
S0390	Smooth muscle, control; re-excision	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0392	Salivary Gland	Salivary gland; normal				pSport1
S0394	Stomach;normal	Stomach; normal				pSport1
S0398	Testis; normal	Testis; normal				pSport1
S0404	Rectum normal	Rectum, normal				pSport1
S0406	Rectum tumour	Rectum tumour				pSport1
S0408	Colon, normal	Colon, normal				pSport1
S0410	Colon, tumour	Colon, tumour				pSport1
S0412	Temporal cortex-Alzheizmer; subtracted	Temporal cortex, alzheimer			disease	Other
S0414	Hippocampus, Alzheimer Subtracted	Hippocampus, Alzheimer Subtracted				Other

S0418	CHME Cell Line;treated 5 hrs	CHME Cell Line; treated				pCMVSport 3.0
S0420	CHME Cell Line,untreated	CHME Cell line, untreatetd				pSport1
S0422	Mo7e Cell Line GM-CSF treated (1ng/ml)	Mo7e Cell Line GM-CSF treated (1ng/ml)				pCMVSport 3.0
S0424	TF-1 Cell Line GM-CSF Treated	TF-1 Cell Line GM-CSF Treated				pSport1
S0426	Monocyte activated; re-excision	Monocyte-activated	blood	Cell Line		Uni-ZAP XR
S0428	Neutrophils control; re-excision	human neutrophils	blood	Cell Line		Uni-ZAP XR
S0430	Aryepiglottis Normal	Aryepiglottis Normal				pSport1
S0432	Sinus piniformis Tumour	Sinus piniformis Tumour				pSport1
S0434	Stomach Normal	Stomach Normal			disease	pSport1
S0436	Stomach Tumour	Stomach Tumour			disease	pSport1
S0438	Liver Normal Met5No	Liver Normal Met5No				pSport1
S0440	Liver Tumour Met 5 Tu	Liver Tumour				pSport1
S0442	Colon Normal	Colon Normal				pSport1
S0444	Colon Tumor	Colon Tumour			disease	pSport1
S0446	Tongue Tumour	Tongue Tumour				pSport1
S0448	Larynx Normal	Larynx Normal				pSport1
S0450	Larynx Tumour	Larynx Tumour				pSport1
S0452	Thymus	Thymus				pSport1
S0454	Placenta	Placenta	Placenta			pSport1
S0456	Tongue Normal	Tongue Normal				pSport1
S0458	Thyroid Normal (SDCA2 No)	Thyroid normal				pSport1
S0460	Thyroid Tumour	Thyroid Tumour				pSport1
S0462	Thyroid Thyroiditis	Thyroid Thyroiditis				pSport1
S0470	Adenocarcinoma	PYFD			disease	pSport1
S0474	Human blood platelets	Platelets	Blood platelets			Other

S0665	Human Amygdala; re-excission	Amygdala				Uni-ZAP XR
S3012	Smooth Muscle Serum Treated, Norm	Smooth muscle	Pulmanary artery	Cell Line		pBluescript
S3014	Smooth muscle, serum induced,re-exc	Smooth muscle	Pulmanary artery	Cell Line		pBluescript
S6014	H. hypothalamus, frac A	Hypothalamus	Brain			ZAP Express
S6022	H. Adipose Tissue	Human Adipose Tissue				Uni-ZAP XR
S6024	Alzheimers, spongy change	Alzheimer"s/Spongy change	Brain		disease	Uni-ZAP XR
S6026	Frontal Lobe, Dementia	Frontal Lobe dementia/Alzheimer"s	Brain			Uni-ZAP XR
S6028	Human Manic Depression Tissue	Human Manic depression tissue	Brain		disease	Uni-ZAP XR
T0002	Activated T-cells	Activated T-Cell, PBL fraction	Blood	Cell Line		pBluescript SK-
T0004	Human White Fat	Human White Fat				pBluescript SK-
T0006	Human Pineal Gland	Human Pinneal Gland				pBluescript SK-
T0010	Human Infant Brain	Human Infant Brain				Other
T0040	HSC172 cells	SA172 Cells				pBluescript SK-
T0041	Jurkat T-cell G1 phase	Jurkat T-cell				pBluescript SK-
T0042	Jurkat T-Cell, S phase	Jurkat T-Cell Line				pBluescript SK-
T0048	Human Aortic Endothelium	Human Aortic Endothilium				pBluescript SK-
T0049	Aorta endothelial cells + TNF-a	Aorta endothelial cells				pBluescript SK-
T0060	Human White Adipose	Human White Fat				pBluescript SK-
T0067	Human Thyroid	Human Thyroid				pBluescript SK-
T0068	Normal Ovary, Premenopausal	Normal Ovary, Premenopausal				pBluescript SK-
T0069	Human Uterus, normal	Human Uterus, normal				pBluescript SK-
T0071	Human Bone Marrow	Human Bone Marrow				pBluescript SK-
T0082	Human Adult Retina	Human Adult Retina				pBluescript SK-
T0103	Human colon carcinoma					pBluescript SK-

	(HCC) cell line					
T0104	HCC cell line metastisis to liver					pBluescript SK-
T0109	Human (HCC) cell line liver (mouse) metastasis, remake					pBluescript SK-
T0110	Human colon carcinoma (HCC) cell line, remake					pBluescript SK-
T0114	Human (Caco-2) cell line, adenocarcinoma, colon, remake					pBluescript SK-
T0115	Human Colon Carcinoma (HCC) cell line					pBluescript SK-
L0005	Clontech human aorta polyA+ mRNA (#6572)					
L0018	Human (M.Lovett)					
L0021	Human adult (K.Okubo)					
L0022	Human adult lung 3" directed MboI cDNA					
L0040	Human colon mucosa					
L0041	Human epidermal keratinocyte					
L0045	Human keratinocyte differential display (B.Lin)					
L0053	Human pancreatic tumor					
L0055	Human promyelocyte					
L0060	Human thymus NSTH II					
L0065	Liver HepG2 cell line.					
L0070	Selected chromosome 21 cDNA library					
L0105	Human aorta polyA+ (TFujiwara)	aorta				

L0142	Human placenta cDNA (TFujiwara)	placenta				
L0157	Human fetal brain (TFujiwara)		brain			
L0163	Human heart cDNA (YNakamura)		heart			
L0183	Human HeLa cells (M.Lovett)			HeLa		
L0194	Human pancreatic cancer cell line Patu 8988t	pancreatic cancer		Patu 8988t		
L0351	Infant brain, Bento Soares					BA, M13-derived
L0352	Normalized infant brain, Bento Soares					BA, M13-derived
L0355	P, Human foetal Brain Whole tissue					Bluescript
L0356	S, Human foetal Adrenals tissue					Bluescript
L0361	Stratagene ovary (#937217)		ovary			Bluescript SK
L0362	Stratagene ovarian cancer (#937219)					Bluescript SK-
L0363	NCI_CGAP_GC2	germ cell tumor				Bluescript SK-
L0364	NCI_CGAP_GC5	germ cell tumor				Bluescript SK-
L0366	Stratagene schizo brain S11	schizophrenic brain S-11 frontal lobe				Bluescript SK-
L0367	NCI_CGAP_Sch1	Schwannoma tumor				Bluescript SK-
L0369	NCI_CGAP_AA1	adrenal adenoma	adrenal gland			Bluescript SK-
L0370	Johnston frontal cortex	pooled frontal lobe	brain			Bluescript SK-
L0371	NCI_CGAP_Br3	breast tumor	breast			Bluescript SK-
L0372	NCI_CGAP_Co12	colon tumor	colon			Bluescript SK-
L0373	NCI_CGAP_Co11	tumor	colon			Bluescript SK-
L0374	NCI_CGAP_Co2	tumor	colon			Bluescript SK-
L0375	NCI_CGAP_Kid6	kidney tumor	kidney			Bluescript SK-

L0376	NCI_CGAP_Lar1	larynx	larynx			Bluescript SK-
L0378	NCI_CGAP_Lu1	lung tumor	lung			Bluescript SK-
L0381	NCI_CGAP_HN4	squamous cell carcinoma	pharynx			Bluescript SK-
L0382	NCI_CGAP_Pr25	epithelium (cell line)	prostate			Bluescript SK-
L0383	NCI_CGAP_Pr24	invasive tumor (cell line)	prostate			Bluescript SK-
L0384	NCI_CGAP_Pr23	prostate tumor	prostate			Bluescript SK-
L0386	NCI_CGAP_HN3	squamous cell carcinoma from base of tongue	tongue			Bluescript SK-
L0387	NCI_CGAP_GCB0	germinal center B-cells	tonsil			Bluescript SK-
L0388	NCI_CGAP_HN6	normal gingiva (cell line from immortalized kerati				Bluescript SK-
L0411	1-NIB					Lafmid BA
L0415	b4HB3MA Cot8-HAP-Ft					Lafmid BA
L0435	Infant brain, LLNL array of Dr. M. Soares 1NIB					lafmid BA
L0438	normalized infant brain cDNA	total brain	brain			lafmid BA
L0439	Soares infant brain 1NIB		whole brain			Lafmid BA
L0454	Clontech adult human fat cell library HL1108A					lambda gt10
L0455	Human retina cDNA randomly primed sublibrary	retina	eye			lambda gt10
L0456	Human retina cDNA Tsp509I-cleaved sublibrary	retina	eye			lambda gt10
L0462	WATM1					lambda gt11
L0463	fetal brain cDNA	brain	brain			lambda gt11
L0471	Human fetal heart, Lambda ZAP Express					Lambda ZAP Express
L0475	KG1-a Lambda Zap Express cDNA library			KG1-a		Lambda Zap Express (Stratagene)
L0476	Fetal brain, Stratagene					Lambda ZAP II

L0480	Stratagene cat#937212 (1992)					Lambda ZAP, pBluescript SK(-)
L0481	CD34+DIRECTIONAL					Lambda ZAPII
L0483	Human pancreatic islet					Lambda ZAPII
L0485	STRATAGENE Human skeletal muscle cDNA library, cat. #936215.	skeletal muscle	leg muscle			Lambda ZAPII
L0493	NCI_CGAP_Ov26	papillary serous carcinoma	ovary			pAMP1
L0497	NCI_CGAP_HSC4	CD34+, CD38- from normal bone marrow donor	bone marrow			pAMP1
L0499	NCI_CGAP_HSC2	stem cell 34+/38+	bone marrow			pAMP1
L0500	NCI_CGAP_Brn20	oligodendroglioma	brain			pAMP1
L0506	NCI_CGAP_Br16	lobullar carcinoma in situ	breast			pAMP1
L0509	NCI_CGAP_Lu26	invasive adenocarcinoma	lung			pAMP1
L0510	NCI_CGAP_Ov33	borderline ovarian carcinoma	ovary			pAMP1
L0511	NCI_CGAP_Ov34	borderline ovarian carcinoma	ovary			pAMP1
L0514	NCI_CGAP_Ov31	papillary serous carcinoma	ovary			pAMP1
L0515	NCI_CGAP_Ov32	papillary serous carcinoma	ovary			pAMP1
L0517	NCI_CGAP_Pr1					pAMP10
L0518	NCI_CGAP_Pr2					pAMP10
L0519	NCI_CGAP_Pr3					pAMP10
L0520	NCI_CGAP_Alv1	alveolar rhabdomyosarcoma				pAMP10
L0521	NCI_CGAP_Ew1	Ewing''s sarcoma				pAMP10
L0522	NCI_CGAP_Kid1	kidney				pAMP10
L0526	NCI_CGAP_Pr12	metastatic prostate bone lesion				pAMP10
L0527	NCI_CGAP_Ov2	ovary				pAMP10
L0528	NCI_CGAP_Pr5	prostate				pAMP10
L0529	NCI_CGAP_Pr6	prostate				pAMP10
L0530	NCI_CGAP_Pr8	prostate				pAMP10
L0532	NCI_CGAP_Thy1	thyroid				pAMP10
L0534	Chromosome 7 Fetal Brain cDNA Library	brain	brain			pAMP10

L0539	Chromosome 7 Placental cDNA Library		placenta			pAMP10
L0540	NCI_CGAP_Pr10	invasive prostate tumor	prostate			pAMP10
L0553	NCI_CGAP_Co22	colonic adenocarcinoma	colon			pAMP10
L0558	NCI_CGAP_Ov40	endometrioid ovarian metastasis	ovary			pAMP10
L0559	NCI_CGAP_Ov39	papillary serous ovarian metastasis	ovary			pAMP10
L0560	NCI_CGAP_HN12	moderate to poorly differentiated invasive carcino	tongue			pAMP10
L0561	NCI_CGAP_HN11	normal squamous epithelium	tongue			pAMP10
L0562	Chromosome 7 HeLa cDNA Library			HeLa cell line; ATCC		pAMP10
L0564	Jia bone marrow stroma	bone marrow stroma				pBluescript
L0565	Normal Human Trabecular Bone Cells	Bone	Hip			pBluescript
L0581	Stratagene liver (#937224)		liver			pBluescript SK
L0586	HTCDL1					pBluescript SK(-)
L0588	Stratagene endothelial cell 937223					pBluescript SK-
L0589	Stratagene fetal retina 937202					pBluescript SK-
L0590	Stratagene fibroblast (#937212)					pBluescript SK-
L0591	Stratagene HeLa cell s3 937216					pBluescript SK-
L0592	Stratagene hNT neuron (#937233)					pBluescript SK-
L0593	Stratagene neuroepithelium (#937231)					pBluescript SK-
L0594	Stratagene					pBluescript SK-

	neuroepithelium NT2RAMI 937234					
L0595	Stratagene NT2 neuronal precursor 937230	neuroepithelial cells	brain			pBluescript SK-
L0596	Stratagene colon (#937204)		colon			pBluescript SK-
L0598	Morton Fetal Cochlea	cochlea	ear			pBluescript SK-
L0599	Stratagene lung (#937210)		lung			pBluescript SK-
L0600	Weizmann Olfactory Epithelium	olfactory epithelium	nose			pBluescript SK-
L0601	Stratagene pancreas (#937208)		pancreas			pBluescript SK-
L0602	Pancreatic Islet	pancreatic islet	pancreas			pBluescript SK-
L0603	Stratagene placenta (#937225)		placenta			pBluescript SK-
L0604	Stratagene muscle 937209	muscle	skeletal muscle			pBluescript SK-
L0605	Stratagene fetal spleen (#937205)	fetal spleen	spleen			pBluescript SK-
L0606	NCI_CGAP_Lym5	follicular lymphoma	lymph node			pBluescript SK-
L0608	Stratagene lung carcinoma 937218	lung carcinoma	lung	NCI-H69		pBluescript SK-
L0611	Schiller meningioma	meningioma	brain			pBluescript SK- (Stratagene)
L0615	22 week old human fetal liver cDNA library					pBluescriptII SK(-)
L0617	Chromosome 22 exon					pBluescriptIIKS+
L0622	HM1					pcDNAII (Invitrogen)
L0623	HM3	pectoral muscle (after mastectomy)				pcDNAII (Invitrogen)
L0625	NCI_CGAP_AR1	bulk alveolar tumor				pCMV-SPORT2
L0629	NCI_CGAP_Mel3	metastatic melanoma to bowel	bowel (skin primary)			pCMV-SPORT4

L0630	NCI_CGAP_CNS1	substantia nigra	brain			pCMV-SPORT4
L0632	NCI_CGAP_Li5	hepatic adenoma	liver			pCMV-SPORT4
L0633	NCI_CGAP_Lu6	small cell carcinoma	lung			pCMV-SPORT4
L0635	NCI_CGAP_PNS1	dorsal root ganglion	peripheral nervous system			pCMV-SPORT4
L0636	NCI_CGAP_Pit1	four pooled pituitary adenomas	brain			pCMV-SPORT6
L0637	NCI_CGAP_Brn53	three pooled meningiomas	brain			pCMV-SPORT6
L0638	NCI_CGAP_Brn35	tumor, 5 pooled (see description)	brain			pCMV-SPORT6
L0639	NCI_CGAP_Brn52	tumor, 5 pooled (see description)	brain			pCMV-SPORT6
L0640	NCI_CGAP_Br18	four pooled high-grade tumors, including two prima	breast			pCMV-SPORT6
L0641	NCI_CGAP_Co17	juvenile granulosa tumor	colon			pCMV-SPORT6
L0642	NCI_CGAP_Co18	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0643	NCI_CGAP_Co19	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0644	NCI_CGAP_Co20	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0645	NCI_CGAP_Co21	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0646	NCI_CGAP_Co14	moderately-differentiated adenocarcinoma	colon			pCMV-SPORT6
L0647	NCI_CGAP_Sar4	five pooled sarcomas, including myxoid liposarcoma	connective tissue			pCMV-SPORT6
L0648	NCI_CGAP_Eso2	squamous cell carcinoma	esophagus			pCMV-SPORT6
L0649	NCI_CGAP_GU1	2 pooled high-grade transitional cell tumors	genitourinary tract			pCMV-SPORT6
L0650	NCI_CGAP_Kid13	2 pooled Wilms" tumors, one primary and one metast	kidney			pCMV-SPORT6
L0651	NCI_CGAP_Kid8	renal cell tumor	kidney			pCMV-SPORT6
L0652	NCI_CGAP_Lu27	four pooled poorly-	lung			pCMV-SPORT6

		differentiated adenocarcinomas				
L0653	NCI_CGAP_Lu28	two pooled squamous cell carcinomas	lung			pCMV-SPORT6
L0654	NCI_CGAP_Lu31		lung, cell line			pCMV-SPORT6
L0655	NCI_CGAP_Lym12	lymphoma, follicular mixed small and large cell	lymph node			pCMV-SPORT6
L0656	NCI_CGAP_Ov38	normal epithelium	ovary			pCMV-SPORT6
L0657	NCI_CGAP_Ov23	tumor, 5 pooled (see description)	ovary			pCMV-SPORT6
L0658	NCI_CGAP_Ov35	tumor, 5 pooled (see description)	ovary			pCMV-SPORT6
L0659	NCI_CGAP_Pan1	adenocarcinoma	pancreas			pCMV-SPORT6
L0661	NCI_CGAP_Mel15	malignant melanoma, metastatic to lymph node	skin			pCMV-SPORT6
L0662	NCI_CGAP_Gas4	poorly differentiated adenocarcinoma with signet r	stomach			pCMV-SPORT6
L0663	NCI_CGAP_Ut2	moderately-differentiated endometrial adenocarcino	uterus			pCMV-SPORT6
L0664	NCI_CGAP_Ut3	poorly-differentiated endometrial adenocarcinoma,	uterus			pCMV-SPORT6
L0665	NCI_CGAP_Ut4	serous papillary carcinoma, high grade, 2 pooled t	uterus			pCMV-SPORT6
L0666	NCI_CGAP_Ut1	well-differentiated endometrial adenocarcinoma, 7	uterus			pCMV-SPORT6
L0667	NCI_CGAP_CML1	myeloid cells, 18 pooled CML cases, BCR/ABL rearra	whole blood			pCMV-SPORT6
L0683	Stanley Frontal NS pool 2	frontal lobe (see description)	brain			pCR2.1-TOPO (Invitrogen)
L0698	Testis 2					PGEM 5zf(+)
L0709	NIH_MGC_21	choriocarcinoma	placenta			pOTB7
L0710	NIH_MGC_7	small cell carcinoma	lung	MGC3		pOTB7
L0717	Gessler Wilms tumor					pSPORT1
L0718	Testis 5					pSPORT1

L0731	Soares_pregnant_uterus_NbHPU		uterus			pT7T3-Pac
L0738	Human colorectal cancer					pT7T3D
L0740	Soares melanocyte 2NbHM	melanocyte				pT7T3D (Pharmacia) with a modified polylinker
L0741	Soares adult brain N2b4HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0742	Soares adult brain N2b5HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0743	Soares breast 2NbHBst		breast			pT7T3D (Pharmacia) with a modified polylinker
L0744	Soares breast 3NbHBst		breast			pT7T3D (Pharmacia) with a modified polylinker
L0745	Soares retina N2b4HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0746	Soares retina N2b5HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0747	Soares_fetal_heart_NbHH19W		heart			pT7T3D (Pharmacia) with a modified polylinker
L0748	Soares fetal liver spleen 1NFLS		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0749	Soares_fetal_liver_spleen_1NFLS_S1		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker

L0750	Soares_fetal_lung_NbHL 19W		lung			pT7T3D (Pharmacia) with a modified polylinker
L0751	Soares ovary tumor NbHOT	ovarian tumor	ovary			pT7T3D (Pharmacia) with a modified polylinker
L0752	Soares_parathyroid_tumor _NbHPA	parathyroid tumor	parathyroid gland			pT7T3D (Pharmacia) with a modified polylinker
L0753	Soares_pineal_gland_N3 HPG		pineal gland			pT7T3D (Pharmacia) with a modified polylinker
L0754	Soares placenta Nb2HP		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0755	Soares_placenta_8to9wee ks_2NbHP8to9W		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0756	Soares_multiple_sclerosis _2NbHMSP	multiple sclerosis lesions				pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0757	Soares_senescent_fibrobla sts_NbHSF	senescent fibroblast				pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0758	Soares_testis_NHT					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0759	Soares_total_fetus_Nb2H F8_9w					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0761	NCI_CGAP_CLL1	B-cell, chronic lymphotic				pT7T3D-Pac

		leukemia				(Pharmacia) with a modified polylinker
L0762	NCI_CGAP_Br1.1	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0763	NCI_CGAP_Br2	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0764	NCI_CGAP_Co3	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0766	NCI_CGAP_GCB1	germinal center B cell				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0767	NCI_CGAP_GC3	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0768	NCI_CGAP_GC4	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0769	NCI_CGAP_Brn25	anaplastic oligodendroglioma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0770	NCI_CGAP_Brn23	glioblastoma (pooled)	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0771	NCI_CGAP_Co8	adenocarcinoma	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0772	NCI_CGAP_Co10	colon tumor RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0773	NCI_CGAP_Co9	colon tumor RER+	colon			pT7T3D-Pac

						(Pharmacia) with a modified polylinker
L0774	NCI_CGAP_Kid3		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0775	NCI_CGAP_Kid5	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0776	NCI_CGAP_Lu5	carcinoid	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0777	Soares_NhHMPu_S1	Pooled human melanocyte, fetal heart, and pregnant	mixed (see below)			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0779	Soares_NFL_T_GBC_S1		pooled			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0780	Soares_NSF_F8_9W_OT_PA_P_S1		pooled			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0782	NCI_CGAP_Pr21	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0783	NCI_CGAP_Pr22	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0784	NCI_CGAP_Lei2	leiomyosarcoma	soft tissue			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0785	Barstead spleen HPLRB2		spleen			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0786	Soares_NbHFB		whole brain			pT7T3D-Pac

						(Pharmacia) with a modified polylinker
L0787	NCI_CGAP_Sub1					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0788	NCI_CGAP_Sub2					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0789	NCI_CGAP_Sub3					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0790	NCI_CGAP_Sub4					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0791	NCI_CGAP_Sub5					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0792	NCI_CGAP_Sub6					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0793	NCI_CGAP_Sub7					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0794	NCI_CGAP_GC6	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0796	NCI_CGAP_Brn50	medulloblastoma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0800	NCI_CGAP_Co16	colon tumor, RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0803	NCI_CGAP_Kid11		kidney			pT7T3D-Pac

						(Pharmacia) with a modified polylinker
L0804	NCI_CGAP_Kid12	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0805	NCI_CGAP_Lu24	carcinoid	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0806	NCI_CGAP_Lu19	squamous cell carcinoma, poorly differentiated (4	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0807	NCI_CGAP_Ov18	fibrotheoma	ovary			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0809	NCI_CGAP_Pr28		prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0811	BATM2					PTZ18
L0946	BT0333		breast			puc18
L1942	HT0452		head_neck			puc18
L2138	ST0186		stomach			puc18
L2251	Human fetal lung	Fetal lung				
L2257	NIH_MGC_65	adenocarcinoma	colon			pCMV-SPORT6
L2258	NIH_MGC_67	retinoblastoma	eye			pCMV-SPORT6
L2260	NIH_MGC_69	large cell carcinoma, undifferentiated	lung			pCMV-SPORT6
L2261	NIH_MGC_70	epithelioid carcinoma	pancreas			pCMV-SPORT6
L2262	NIH_MGC_72	melanotic melanoma	skin			pCMV-SPORT6
L2263	NIH_MGC_66	adenocarcinoma	ovary			pCMV-SPORT6
L2265	NIH_MGC_39	adenocarcinoma	pancreas			pOTB7
L2270	Lupski_dorsal_root_gangl ion	dorsal root ganglia				pCMV-SPORT6 (Life Technologies)
L2333	CT0417		colon			puc18

L2338	CT0432		colon			puc18
L2346	CT0483		colon			puc18
L2400	NN0116		nervous_normal			puc18
L2439	NN1022		nervous_normal			puc18
L2477	HT0408		head_neck			puc18
L2490	HT0545		head_neck			puc18
L2495	HT0594		head_neck			puc18
L2504	HT0636		head_neck			puc18
L2522	HT0704		head_neck			puc18
L2540	HT0728		head_neck			puc18
L2562	HT0760		head_neck			puc18
L2634	HT0872		head_neck			puc18
L2651	NIH_MGC_20	melanotic melanoma	skin			pOTB7
L2653	NIH_MGC_58	hypernephroma	kidney			pDNR-LIB (Clontech)
L2654	NIH_MGC_9	adenocarcinoma cell line	ovary			pOTB7
L2655	NIH_MGC_55	from acute myelogenous leukemia	bone marrow			pDNR-LIB (Clontech)
L2657	NIH_MGC_54	from chronic myelogenous leukemia	bone marrow			pDNR-LIB (Clontech)
L2702	NT0098		nervous_tumor			puc18
L2804	FT0103		prostate_tumor			puc18
L2854	UM0091		uterus			puc18
L2884	AN0041		amnion_normal			puc18
L2906	BN0047		breast_normal			puc18
L3002	BN0276		breast_normal			puc18
L3019	BN0303		breast_normal			puc18
L3081	ET0005		lung_tumor			puc18
L3089	ET0018		lung_tumor			puc18
L3092	ET0023		lung_tumor			puc18
L3127	ET0084		lung_tumor			puc18
L3140	MT0031		marrow			puc18

L3154	MT0050		marrow			puc18
L3212	OT0076		ovary			puc18
L3215	OT0083		ovary			puc18
L3255	FN0064		prostate_normal			puc18
L3316	FN0188		prostate_normal			puc18
L3352	TN0027		testis_normal			puc18
L3374	TN0070		testis_normal			puc18
L3388	GKC	hepatocellular carcinoma				pBluescript sk(-)
L3391	NIH_MGC_53	carcinoma, cell line	bladder			pDNR-LIB (Clontech)
L3504	HT0873		head_neck			puc18
L3521	HT0919		head_neck			puc18
L3603	UM0093		uterus			puc18
L3612	UT0011		uterus_tumor			puc18
L3636	NIH_MGC_73		brain			pDNR-LIB (Clontech)
L3643	ADB	Adrenal gland				pBluescript sk(-)
L3645	Cu	adrenal cortico adenoma for Cushing"s syndrome				pBluescript sk(-)
L3649	DCB					pTriplEx2
L3655	HTC	Hypothalamus				pBluescript sk(-)
L3657	HTF	Hypothalamus				pBluescript sk(-)
L3658	cdA	pheochromocytoma				pTriplEx2
L3659	CB	cord blood				pBluescript
L3811	NPC	pituitary				pBluescript sk(-)
L3815	MDS	Bone marrow				pTriplEx2
L3817	HEMBB1	whole embryo, mainly body				pME18SFL3
L3823	NT2RM1			NT2		pUC19FL3
L3827	NT2RP2			NT2		pME18SFL3
L3828	NT2RP3			NT2		pME18SFL3
L3829	NT2RP4			NT2		pME18SFL3
L3831	OVARC1	ovary, tumor tissue				pME18SFL3

L3832	PLACE1	placenta				pME18SFL3
L3833	PLACE2	placenta				pME18SFL3
L3872	NCI_CGAP_Skn1		skin, normal, 4 pooled sa			pCMV-SPORT6
L3904	NCI_CGAP_Brn64	glioblastoma with EGFR amplification	brain			pCMV-SPORT6
L3905	NCI_CGAP_Brn67	anaplastic oligodendroglioma with 1p/19q loss	brain			pCMV-SPORT6
L4497	NCI_CGAP_Br22	invasive ductal carcinoma, 3 pooled samples	breast			pCMV-SPORT6
L4501	NCI_CGAP_Sub8					pT7T3D-Pac (Pharmacia) with a modified polylinker
L4556	NCI_CGAP_HN13	squamous cell carcinoma	tongue			pCMV-SPORT6
L4669	NCI_CGAP_Ov41	serous papillary tumor	ovary			pCMV-SPORT6
L4747	NCI_CGAP_Brn41	oligodendroglioma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L5565	NCI_CGAP_Brn66	glioblastoma with probably TP53 mutation and witho	brain			pCMV-SPORT6
L5566	NCI_CGAP_Brn70	anaplastic oligodendroglioma	brain			pCMV-SPORT6.ccdb
L5574	NCI_CGAP_HN19	normal epithelium	nasopharynx			pAMP10
L5575	NCI_CGAP_Brn65	glioblastoma without EGFR amplification	brain			pCMV-SPORT6
L5622	NCI_CGAP_Skn3		skin			pCMV-SPORT6
L5623	NCI_CGAP_Skn4	squamous cell carcinoma	skin			pCMV-SPORT6

Description of Table 5

Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 1B.1, column 9. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). Column 2 provides diseases associated with the cytologic band disclosed in Table 1B.1, column 8, as determined using the Morbid Map database.

Table 5

OMIM Reference	Description
101000	Meningioma, NF2-related, sporadic Schwannoma, sporadic
101000	Neurofibromatosis, type 2
101000	Neurolemmomatosis
101000	Malignant mesothelioma, sporadic
102200	Somatotrophinoma
102772	[AMP deaminase deficiency, erythrocytic]
103600	[Dysalbuminemic hyperthyroxinemia]
103600	[Dysalbuminemic hyperzincemia], 194470
103600	Analbuminemia
103850	Aldolase A deficiency
104150	[AFP deficiency, congenital]
104150	[Hereditary persistence of alpha-fetoprotein]
104500	Amelogenesis imperfecta-2, hypoplastic local type
104770	Amyloidosis, secondary, susceptibility to
106100	Angioedema, hereditary
106210	Peters anomaly
106210	Cataract, congenital, with late-onset corneal dystrophy
106210	Foveal hypoplasia, isolated, 136520
106210	Aniridia
107271	CD59 deficiency
107300	Antithrombin III deficiency
107670	Apolipoprotein A-II deficiency
110700	Vivax malaria, susceptibility to
112261	Fibrodysplasia ossificans progressiva
114550	Hepatocellular carcinoma
114835	Monocyte carboxyesterase deficiency
115500	Acatalasemia
116800	Cataract, Marner type
116806	Colorectal cancer
116860	Cavernous angiomatous malformations
118485	Polycystic ovary syndrome with hyperandrogenemia
120070	Alport syndrome, autosomal recessive, 203780
120131	Alport syndrome, autosomal recessive, 203780
120131	Hematuria, familial benign
120140	Osteoarthrosis, precocious

120140	SED congenita
120140	SMED Strudwick type
120140	Stickler syndrome, type I
120140	Wagner syndrome, type II
120140	Achondrogenesis-hypochondrogenesis, type II
120140	Kniest dysplasia
120220	Bethlem myopathy, 158810
120240	Bethlem myopathy, 158810
120260	Epiphyseal dysplasia, multiple, type 2, 600204
120550	C1q deficiency, type A
120570	C1q deficiency, type B
120575	C1q deficiency, type C
121800	Corneal dystrophy, crystalline, Schnyder
123000	Craniometaphyseal dysplasia
123580	Cataract, congenital, autosomal dominant
123620	Cataract, cerulean, type 2, 601547
126060	Anemia, megaloblastic, due to DHFR deficiency
126090	Hyperphenylalaninemia due to pterin-4a-carbinolamine dehydratase deficiency, 264070
126337	Myxoid liposarcoma
126600	Doyne honeycomb retinal dystrophy
126600	Drusen, radial, autosomal dominant
129010	Neuropathy, congenital hypomyelinating, 1
129900	EEC syndrome-1
130500	Elliptocytosis-1
131100	Multiple endocrine neoplasia I
131100	Prolactinoma, hyperparathyroidism, carcinoid syndrome
131100	Carcinoid tumor of lung
131210	Atherosclerosis, susceptibility to
133200	Erythrokeratodermia variabilis
133701	Exostoses, multiple, type 2
133780	Vitreoretinopathy, exudative, familial
135940	Ichthyosis vulgaris, 146700
136132	[Fish-odor syndrome], 602079
136435	Ovarian dysgenesis, hypergonadotropic, with normal karyotype, 233300
136530	Male infertility, familial
138030	[Hyperproglucagonemia]
138140	Glucose transport defect, blood-brain barrier
138760	[Glyoxalase II deficiency]
138981	Pulmonary alveolar proteinosis, 265120
140100	[Anhaptoglobinemia]
140100	[Hypohaptogloginemia]
142600	Hemolytic anemia due to hexokinase deficiency
143200	Wagner syndrome
143200	Erosive vitreoretinopathy
145001	Hyperparathyroidism-jaw tumor syndrome
146760	[IgG receptor I, phagocytic, familial deficiency of]
146790	Lupus nephritis, susceptibility to
147050	Atopy
148900	Klippel-Feil syndrome with laryngeal malformation
151385	Leukemia, acute myeloid
151390	Leukemia, acute T-cell

151670	Hepatic lipase deficiency
152445	Vohwinkel syndrome, 124500
152445	Erythrokeratoderma, progressive symmetric, 602036
153700	Macular dystrophy, vitelliform type
154545	Chronic infections, due to opsonin defect
155555	[Red hair/fair skin]
155555	UV-induced skin damage, vulnerability to
159001	Muscular dystrophy, limb-girdle, type 1B
160980	Carney myxoma-endocrine complex
161015	Mitochondrial complex I deficiency, 252010
164009	Leukemia, acute promyelocytic, NUMA/RARA type
164500	Spinocerebellar ataxia-7
164920	Piebaldism
164920	Mast cell leukemia
164920	Mastocytosis with associated hematologic disorder
168461	Multiple myeloma, 254250
168461	Parathyroid adenomatosis 1
168461	Centrocytic lymphoma
168468	Metaphyseal chondrodysplasia, Murk Jansen type, 156400
168500	Parietal foramina
170650	Periodontitis, juvenile
171650	Lysosomal acid phosphatase deficiency
171760	Hypophosphatasia, adult, 146300
171760	Hypophosphatasia, infantile, 241500
171860	Hemolytic anemia due to phosphofructokinase deficiency
173610	Platelet alpha/delta storage pool deficiency
174000	Medullary cystic kidney disease, AD
174810	Osteolysis, familial expansile
176640	Creutzfeldt-Jakob disease, 123400
176640	Gerstmann-Straussler disease, 137440
176640	Insomnia, fatal familial
176880	Protein S deficiency
176930	Dysprothrombinemia
176930	Hypoprothrombinemia
178300	Ptosis, hereditary congenital, 1
179615	Reticulosis, familial histiocytic, 267700
179615	Severe combined immunodeficiency, B cell-negative, 601457
179616	Severe combined immunodeficiency, B cell-negative, 601457
179755	Renal cell carcinoma, papillary, 1
180105	Retinitis pigmentosa-10
180200	Osteosarcoma, 259500
180200	Pinealoma with bilateral retinoblastoma
180200	Retinoblastoma
180200	Bladder cancer, 109800
180385	Leukemia, acute T-cell
180721	Retinitis pigmentosa, digenic
180840	Susceptibility to IDDM
181510	Schizophrenia
182280	Small-cell cancer of lung
182860	Pyropoikilocytosis
182860	Spherocytosis, recessive
182860	Elliptocytosis-2

186580	Arthrocutaneouveal granulomatosis
188826	Sorsby fundus dystrophy, 136900
189800	Preeclampsia/eclampsia
190685	Down syndrome
191181	Cervical carcinoma
191315	Insensitivity to pain, congenital, with anhidrosis, 256800
192090	Ovarian carcinoma
192090	Breast cancer, lobular
192090	Endometrial carcinoma
192090	Gastric cancer, familial, 137215
193235	Vitreoretinopathy, neovascular inflammatory
193300	Renal cell carcinoma
193300	von Hippel-Lindau syndrome
194070	Wilms tumor, type 1
194070	Denys-Drash syndrome
194070	Frasier syndrome, 136680
208400	Aspartylglucosaminuria
209901	Bardet-Biedl syndrome 1
212138	Carnitine-acylcarnitine translocase deficiency
216550	Cohen syndrome
222800	Hemolytic anemia due to bisphosphoglycerate mutase deficiency
222900	Sucrose intolerance
227646	Fanconi anemia, type D
227650	Fanconi anemia, type A
230800	Gaucher disease
230800	Gaucher disease with cardiovascular calcification
231675	Glutaricaciduria, type IIC
231680	Glutaricaciduria, type IIA
232500	Glycogen storage disease IV
232600	McArdle disease
233700	Chronic granulomatous disease due to deficiency of NCF-1
236100	Holoprosencephaly-1
236200	Homocystinuria, B6-responsive and nonresponsive types
236700	McKusick-Kaufman syndrome
240300	Autoimmune polyglandular disease, type I
245349	Lacticacidemia due to PDX1 deficiency
245900	Norum disease
245900	Fish-eye disease
249100	Familial Mediterranean fever
250850	Hypermethioninemia, persistent, autosomal dominant, due to methionine adenosyltransferase I/III deficiency
253000	Mucopolysaccharidosis IVA
253200	Maroteaux-Lamy syndrome, several forms
255800	Schwartz-Jampel syndrome
259700	Osteopetrosis, recessive
259770	Osteoporosis-pseudoglioma syndrome
259900	Hyperoxaluria, primary, type 1
266200	Anemia, hemolytic, due to PK deficiency
266600	Inflammatory bowel disease-1
267750	Knobloch syndrome
268800	Sandhoff disease, infantile, juvenile, and adult forms
268800	Spinal muscular atrophy, HEXB-related

272800	Tay-Sachs disease
272800	[Hex A pseudodeficiency]
272800	GM2-gangliosidosis, juvenile, adult
274180	Thromboxane synthase deficiency
276600	Tyrosinemia, type II
276700	Tyrosinemia, type I
300011	Menkes disease, 309400
300011	Occipital horn syndrome, 304150
300011	Cutis laxa, neonatal
300046	Mental retardation, X-linked 23, nonspecific
300047	Mental retardation, X-linked 20
300067	Subcortical laminar heterotopia, X-linked dominant
300067	Lissencephaly, X-linked
300071	Night blindness, congenital stationary, type 2
300075	Coffin-Lowry syndrome, 303600
300077	Mental retardation, X-linked 29
300110	Night blindness, congenital stationary, X-linked incomplete, 300071
300121	Subcortical laminal heteropia, X-linked, 300067
300121	Lissencephaly, X-linked, 300067
300127	Mental retardation, X-linked, 60
300600	Ocular albinism, Forsius-Eriksson type
301000	Thrombocytopenia, X-linked, 313900
301000	Wiskott-Aldrich syndrome
301200	Amelogenesis imperfecta
301201	Amelogenesis imperfecta-3, hypoplastic type
301830	Arthrogryposis, X-linked (spinal muscular atrophy, infantile, X-linked)
301835	Arts syndrome
302350	Nance-Horan syndrome
302801	Charcot-Marie-Tooth neuropathy, X-linked-2, recessive
305435	Heterocellular hereditary persistence of fetal hemoglobin, Swiss type
305450	FG syndrome
306000	Glycogenosis, X-linked hepatic, type I
306000	Glycogenosis, X-linked hepatic, type II
307800	Hypophosphatemia, hereditary
308800	Keratosis follicularis spinulosa decalvans
309470	Mental retardation, X-linked, syndromic-3, with spastic diplegia
309500	Renpenning syndrome-1
309510	Mental retardation, X-linked, syndromic-1, with dystonic movements, ataxia, and seizures
309605	Mental retardation, X-linked, syndromic-4, with congenital contractures and low fingertip arches
309610	Mental retardation, X-linked, syndromic-2, with dysmorphism and cerebral atrophy
309850	Brunner syndrome
311050	Optic atrophy, X-linked
311200	Oral-facial-digital syndrome 1
311850	Phosphoribosyl pyrophosphate synthetase-related gout
312040	N syndrome, 310465
312060	Properdin deficiency, X-linked
312170	Pyruvate dehydrogenase deficiency
312700	Retinoschisis
313400	Spondyloepiphyseal dysplasia tarda

313700	Perineal hypospadias
313700	Prostate cancer
313700	Spinal and bulbar muscular atrophy of Kennedy, 313200
313700	Breast cancer, male, with Reifenstein syndrome
313700	Androgen insensitivity, several forms
314580	Wieacker-Wolff syndrome
600045	Xeroderma pigmentosum, group E, subtype 2
600065	Leukocyte adhesion deficiency, 116920
600079	Colon cancer
600151	Bardet-Biedl syndrome 3
600163	Long QT syndrome-3
600223	Spinocerebellar ataxia-4
600319	Diabetes mellitus, insulin-dependent, 4
600354	Spinal muscular atrophy-1, 253300
600354	Spinal muscular atrophy-2, 253550
600354	Spinal muscular atrophy-3, 253400
600359	Bartter syndrome, type 2
600374	Bardet-Biedl syndrome 4
600528	CPT deficiency, hepatic, type I, 255120
600623	Prostate cancer, 176807
600631	Enuresis, nocturnal, 1
600678	Cancer susceptibility
600760	Pseudohypoaldosteronism, type I, 264350
600760	Liddle syndrome, 177200
600761	Pseudohypoaldosteronism, type I, 264350
600761	Liddle syndrome, 177200
600795	Dementia, familial, nonspecific
600808	Enuresis, nocturnal, 2
600811	Xeroderma pigmentosum, group E, DDB-negative subtype, 278740
600850	Schizophrenia disorder-4
600882	Charcot-Marie-Tooth neuropathy-2B
600887	Endometrial carcinoma
600897	Cataract, zonular pulverulent-1, 116200
600900	Muscular dystrophy, limb-girdle, type 2E
600958	Cardiomyopathy, familial hypertrophic, 4, 115197
600975	Glaucoma 3, primary infantile, B
601072	Deafness, autosomal recessive 8
601105	Pycnodysostosis, 265800
601145	Epilepsy, progressive myoclonic 1, 254800
601284	Hereditary hemorrhagic telangiectasia-2, 600376
601362	DiGeorge syndrome/velocardiofacial syndrome complex-2
601386	Deafness, autosomal recessive 12
601412	Deafness, autosomal dominant 7
601493	Cardiomyopathy, dilated 1C
601567	Combined factor V and VIII deficiency, 227300
601652	Glaucoma 1A, primary open angle, juvenile-onset, 137750
601669	Hirschsprung disease, one form
601769	Osteoporosis, involutional
601769	Rickets, vitamin D-resistant, 277440
601780	Ceroid-lipofuscinosis, neuronal-6, variant late infantile
601863	Bare lymphocyte syndrome, complementation group C
601884	[High bone mass]

601920	Alagille syndrome, 118450
602080	Paget disease of bone-2
602092	Deafness, autosomal recessive 18
602116	Glioma
602491	Hyperlipidemia, familial combined, 1
602568	Homocystinuria-megaloblastic anemia,.cbl E type, 236270
602574	Deafness, autosomal dominant 12, 601842
602574	Deafness, autosomal dominant 8, 601543
602783	Spastic paraplegia-7

Mature Polypeptides

The present invention also encompasses mature forms of a polypeptide having the amino acid sequence of SEQ ID NO:Y and/or the amino acid sequence encoded by the cDNA in a deposited clone. Polynucleotides encoding the mature forms (such as, for example, the polynucleotide sequence in SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone) are also encompassed by the invention. Moreover, fragments or variants of these polypeptides (such as, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of the polynucleotide encoding these polypeptides) are also encompassed by the invention. In preferred embodiments, these fragments or variants retain one or more functional acitivities of the full-length or mature form of the polypeptide (e.g., biological activity (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal disorders), antigenicity (ability to bind, or compete with a polypeptide of the invention for binding, to an anti-polypeptide of the invention antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention). Antibodies that bind the polypeptides of the invention, and polynucleotides encoding these polypeptides are also encompassed by the invention.

According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretary leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species of the protein. Further, it has long been known that cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide.

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-

286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1A.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the predicted mature form of the polypeptide as delineated in columns 14 and 15 of Table 1A. Moreover, fragments or variants of these polypeptides (such as, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of the polynucleotide encoding these polypeptides) are also encompassed by the invention. In preferred embodiments, these fragments or variants retain one or more functional acitivities of the full-length or mature form of the polypeptide (e.g., biological activity (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal disorders), antigenicity (ability to bind, or compete with a polypeptide of the invention for binding, to an anti-polypeptide of the invention antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention). Antibodies that bind the polypeptides of the invention, and polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotides encoding proteins comprising, or consisting of, the predicted mature form of polypeptides of the invention (e.g., polynucleotides having the sequence of SEQ ID NO: X (Table 1A, column 4), the sequence delineated in columns 7 and 8 of Table 1A, and a sequence encoding the mature polypeptide delineated in columns 14 and 15 of Table 1A (e.g., the sequence of SEQ ID NO:X encoding the mature polypeptide delineated in columns 14 and 15 of Table 1)) are also encompassed by the invention, as are fragments or variants of these polynucleotides (such as, fragments as described herein, polynucleotides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%,

99%, or 100% identical to these polyncueotides, and nucleic acids which hybridizes under stringent conditions to the complementary strand of the polynucleotide).

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 15 residues of the predicted cleavage point (i.e., having 1, 2, 3, 4, 5, 6, 7, 8 , 9, 10, 11, 12, 13, 14, or 15 more or less contiguous residues of SEQ ID NO:Y at the N-terminus when compared to the predicted mature form of the polypeptide (e.g., the mature polypeptide delineated in columns 14 and 15 of Table 1). Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. Nonetheless, the present invention provides the mature protein produced by expression of the polynucleotide sequence of SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone, in a mammalian cell (e.g., COS cells, as desribed below). These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Polynucleotide and Polypeptide Variants

The present invention is also directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, nucleotide sequences encoding the polypeptide of SEQ ID NO:Y, the nucleotide sequence of SEQ ID NO:X that encodes the polypeptide sequence as defined in columns 13 and 14 of Table 1A, nucleotide sequences encoding the polypeptide sequence as defined in columns 13 and 14 of Table 1A, the nucleotide sequence of SEQ ID NO:X encoding the polypeptide sequence as defined in Table 1B, the nucleotide sequence as defined in columns 8 and 9 of Table 2, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, the nucleotide sequence as defined in column 6 of Table 1C, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in column 6 of Table 1C, the cDNA sequence contained in ATCC Deposit No:Z, nucleotide sequences encoding the polypeptide encoded by the cDNA sequence contained in ATCC Deposit No:Z, and/or nucleotide sequences encoding a mature (secreted) polypeptide encoded by the cDNA sequence contained in ATCC Deposit No:Z.

The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y, the polypeptide as defined in columns 13 and 14 of Table 1A, the polypeptide sequence as defined in columns 6 and 7 of Table 1B.1, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, a polypeptide sequence encoded by the nucleotide sequence as defined in column 6 of Table 1C, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, the polypeptide sequence encoded by the cDNA sequence contained in ATCC Deposit No:Z and/or a mature (secreted) polypeptide encoded by the cDNA sequence contained in ATCC Deposit No:Z.

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence described in SEQ ID NO:X or contained in the cDNA sequence of ATCC Deposit No:Z; (b) a nucleotide sequence in SEQ ID NO:X or the cDNA in ATCC Deposit No:Z which encodes the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; (c) a nucleotide sequence in SEQ ID NO:X or the cDNA in ATCC Deposit No:Z which encodes a mature polypeptide (i.e., a secreted polypeptide (e.g., as delineated in columns 14 and 15 of Table 1A)); (d) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of ATCC Deposit No:Z, which encodes a biologically active fragment of a polypeptide; (e) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of ATCC Deposit No:Z, which encodes an antigenic fragment of a polypeptide; (f) a nucleotide sequence encoding a polypeptide comprising the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; (g) a nucleotide sequence encoding a mature polypeptide of the amino acid sequence of SEQ ID NO:Y (i.e., a secreted polypeptide (e.g., as delineated in columns 14 and 15 of Table 1A)) or a mature polypeptide of the amino acid sequence encoded by the cDNA in ATCC Deposit No:Z ; (h) a nucleotide sequence encoding a biologically active fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; (i) a nucleotide sequence encoding an antigenic fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; and (j) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above.

The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (i), or (j) above, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the cDNA contained in ATCC Deposit No:Z or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, the nucleotide coding sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, the nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto, the nucleotide sequence in SEQ ID NO:X encoding the polypeptide sequence as defined in columns 6 and 7 of Table 1B.1 or the complementary strand thereto, nucleotide sequences encoding the polypeptide as defined in column 6 and 7 of Table 1B.1 or the complementary strand thereto, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides and nucleic acids.

In a preferred embodiment, the invention encompasses nucleic acid molecules which comprise, or alternatively, consist of a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under lower stringency conditions, to a polynucleotide in (a), (b), (c), (d), (e), (f), (g), (h), or (i), above, as are polypeptides encoded by these polynucleotides. In another preferred embodiment, polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

In another embodiment, the invention provides a purified protein comprising, or alternatively consisting of, a polypeptide having an amino acid sequence selected from the group consisting of: (a) the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; (b) the amino acid sequence of a mature (secreted) form of a polypeptide having the amino acid sequence of SEQ ID NO:Y (e.g., as

delineated in columns 14 and 15 of Table 1A) or a mature form of the amino acid sequence encoded by the cDNA in ATCC Deposit No:Z mature; (c) the amino acid sequence of a biologically active fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; and (d) the amino acid sequence of an antigenic fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z.

The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the amino acid sequences in (a), (b), (c), or (d), above, the amino acid sequence shown in SEQ ID NO:Y, the amino acid sequence encoded by the cDNA contained in ATCC Deposit No:Z, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C, the amino acid sequence as defined in columns 6 and 7 of Table 1B.1, an amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X, and an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further proteins encoded by polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these amino acid sequences under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are the polynucleotides encoding these proteins.

By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence referred to in Table 1B or 2 as the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be

determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide

sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of a polypeptide referred to in Table 1A (e.g., the amino acid sequence delineated in columns 14 and 15) or a fragment thereof, Table 1B.1 (e.g., the amino acid sequence identified in column 6) or a fragment thereof, Table 2 (e.g., the amino acid sequence of the polypeptide encoded by the polynucleotide sequence defined in columns 8 and 9 of Table 2) or a fragment thereof, the amino acid sequence of the polypeptide encoded by the polynucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C or a fragment thereof, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence of the polypeptide encoded by cDNA contained in ATCC Deposit No:Z, or a fragment thereof, the amino acid sequence of a mature (secreted) polypeptide encoded by cDNA contained in ATCC Deposit No:Z, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases

of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequnce are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as E. coli).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985)). These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention.

Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. As an example, Ron et al. (J. Biol. Chem. 268: 2984-2988 (1993)) reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem. 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show a biological or functional activity of the polypeptides of the invention (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating cardiovascular disorders). Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, (e.g., encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even

where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); (3) Northern Blot analysis for detecting mRNA expression in specific tissues (e.g., normal or diseased tissues); and (4) *in situ* hybridization (e.g., histochemistry) for detecting mRNA expression in specific tissues (e.g., normal or diseased tissues).

Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having functional activity. By a polypeptide having "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein and/or a mature (secreted) protein of the invention. Such functional activities include, but are not limited to, biological activity (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal diseases and disorders), antigenicity (ability to bind, or compete with a polypeptide of the invention for binding, to an anti-polypeptide of the invention antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

The functional activity of the polypeptides, and fragments, variants and derivatives of the invention, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with a full-length polypeptide of the present invention for binding to an anti-polypetide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is

labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, the ability of physiological correlates of a polypeptide of the present invention to bind to a substrate(s) of the polypeptide of the invention can be routinely assayed using techniques known in the art.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants and derivatives thereof to elicit polypeptide related biological activity (either *in vitro* or *in vivo*). Other methods will be known to the skilled artisan and are within the scope of the invention.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA contained in ATCC Deposit No:Z, the nucleic acid sequence referred to in Table 1B (SEQ ID NO:X), the nucleic acid sequence disclosed in Table 1A (e.g., the nucleic acid sequence delineated in columns 7 and 8), the nucleic acid sequence disclosed in Table 2 (e.g., the nucleic acid sequence delineated in columns 8 and 9) or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for

protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham and Wells, Science 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitutions with one or more of the amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, serum albumin (preferably human serum albumin) or a fragment thereof, or leader or secretory sequence, or a sequence facilitating purification, or (v) fusion of the polypeptide with another compound, such as albumin (including but not limited to recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See

Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

A further embodiment of the invention relates to polypeptides which comprise the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions from a polypeptide sequence disclosed herein. Of course it is highly preferable for a polypeptide to have an amino acid sequence which, for example, comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, the amino acid sequence of the mature (e.g., secreted) polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columnns 8 and 9 of Table 2, an amino acid sequence encoded by the complement of SEQ ID NO:X, an amino acid sequence encoded by cDNA contained in ATCC Deposit No:Z, and/or the amino acid sequence of a mature (secreted) polypeptide encoded by cDNA contained in ATCC Deposit No:Z, or a fragment thereof, which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions.

In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of a reference amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature formand/or other fragments described herein); (b) the amino acid sequence encoded by SEQ ID NO:X or fragments thereof; (c) the amino acid sequence encoded by the complement of SEQ ID NO:X or fragments thereof; (d) the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or fragments thereof; and (e) the amino acid sequence encoded by cDNA contained in ATCC Deposit No:Z or fragments thereof; wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid substitutions are conservative. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotide and Polypeptide Fragments

The present invention is also directed to polynucleotide fragments of the polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers to a polynucleotide having a nucleic acid sequence which, for example: is a portion of the cDNA contained in ATCC Deposit No:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in ATCC Deposit No:Z or the complementary strand thereto; is a portion of the polynucleotide sequence

encoding the mature (secreted) polypeptide encoded by the cDNA contained in ATCC Deposit No:Z or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the mature amino acid sequence as defined in columns 14 and 15 of Table 1A or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X; is a polynucleotide sequence encoding a portion of a polypeptide encoded by the complement of the polynucleotide sequence in SEQ ID NO:X; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto; or is a portion of the polynucleotide sequence of SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto.

The polynucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in ATCC Deposit No:Z, or the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 160, 170, 180, 190, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-

3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity; such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal diseases and disorders). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

Further representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-

7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of the cDNA sequence contained in ATCC Deposit No:Z, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence delineated in Table 1C column 6. Additional, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence that is the complementary strand of a sequence délineated in column 6 of Table 1C. In further embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated Table 1C, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1C, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1C which correspond to the same ATCC Deposit No:Z (see Table 1C, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A, 1B, or 1C) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in the same row of column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A, 1B, or 1C) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X (e.g., as described herein) are directly contiguous Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one

of the sequences delineated in column 6 of Table 1C are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1C, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of the amino acid sequence contained in SEQ ID NO:Y, is a portion of the mature form of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, a portion of an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columnns 8 and 9 of Table 2, is a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, is a portion of an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, is a portion of the amino acid sequence of a mature (secreted) polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or is a portion of an amino acid sequence encoded by the cDNA contained in ATCC Deposit No:Z. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760,

761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of cDNA and SEQ ID NO: Y. In a preferred embodiment, polypeptide fragments of the invention include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities; such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal diseases and disorders; ability to multimerize; ability to bind a ligand; antigenic ability useful for production of polypeptide specific antibodies) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both.

For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide as defined in columns 14 and 15 of Table 1A, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X or the complement thereof, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1C, a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or a mature polypeptide encoded by the cDNA contained in ATCC Deposit No:Z). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, or the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1C, a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or a mature polypeptide encoded by the cDNA contained in ATCC Deposit No:Z). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2),

the cDNA contained in ATCC Deposit No:Z, and/or the complement thereof, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal diseases and disorders; ability to multimerize; ability to bind a ligand; antigenic ability useful for production of polypeptide specific antibodies) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Any polypeptide sequence encoded by, for example, the polynucleotide sequences set forth as SEQ ID NO:X or the complement thereof, (presented, for example, in Tables 1A and 2), the cDNA contained in ATCC Deposit No:Z, or the polynucleotide sequence as defined in column 6 of Table 1C, may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X (e.g., the polypeptide of SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columnns 8 and 9 of Table 2) or the cDNA contained in ATCC Deposit No:Z may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; http://www.dnastar.com/).

Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle hydrophilic regions and hydrophobic regions; Eisenberg alpha- and

beta-amphipathic regions; Karplus-Schulz flexible regions; Emini surface-forming regions; and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a functional activity (e.g. biological activity such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating gastrointestinal diseases and disorders; ability to multimerize; ability to bind a ligand; antigenic ability useful for production of polypeptide specific antibodies) of the polypeptide sequence of which the amino acid sequence is a fragment. By a polypeptide displaying a "functional activity" is meant a polypeptide capable of one or more known functional activities associated with a full-length protein, such as, for example, biological activity, antigenicity, immunogenicity, and/or multimerization, as described herein.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Epitopes and Antibodies

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of: the polypeptide sequence shown in SEQ ID NO:Y; a polypeptide sequence encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2; the polypeptide sequence encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1C

or the complement thereto; the polypeptide sequence encoded by the cDNA contained in ATCC Deposit No:Z; or the polypeptide sequence encoded by a polynucleotide that hybridizes to the sequence of SEQ ID NO:X, the complement of the sequence of SEQ ID NO:X, the complement of a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, or the cDNA sequence contained in ATCC Deposit No:Z under stringent hybridization conditions or alternatively, under lower stringency hybridization as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X, or a fragment thereof), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions defined *supra*.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes.

Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Non-limiting examples of epitopes of polypeptides that can be used to generate antibodies of the invention include a polypeptide comprising, or alternatively consisting of, at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y specified in column 6 of Table 1B.1. These polypeptide fragments have been determined to bear antigenic epitopes of the proteins of the invention by the analysis of the Jameson-Wolf antigenic index which is included in the DNAStar suite of computer programs. By "comprise" it is intended that a polypeptide contains at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y shown in column 6 of Table 1B.1, but it may contain additional flanking residues on either the amino or carboxyl termini of the recited portion. Such additional flanking sequences are preferably sequences naturally found adjacent to the portion; i.e., contiguous sequence shown in SEQ ID NO:Y. The flanking sequence may, however, be sequences from a heterolgous polypeptide, such as from another protein described herein or from a heterologous polypeptide not described herein. In particular embodiments, epitope portions of a polypeptide of the invention comprise one, two, three, or more of the portions of SEQ ID NO:Y shown in column 6 of Table 1B.1.

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde.

Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 μg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

Such fusion proteins as those described above may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG

or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin (HA) tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, Proc. Natl. Acad. Sci. USA 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni2+ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Fusion Proteins

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

In certain preferred embodiments, proteins of the invention are fusion proteins comprising an amino acid sequence that is an N and/or C- terminal deletion of a polypeptide of the invention. In preferred embodiments, the invention is directed to a fusion protein comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence of the invention. Polynucleotides encoding these proteins are also encompassed by the invention.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

As one of skill in the art will appreciate that, as discussed above, polypeptides of the present invention, and epitope-bearing fragments thereof, can be combined with heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), or albumin (including, but not limited to, native or recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties (EP-A 0232 262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a polypeptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)).

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment,

alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Recombinant and Synthetic Production of Polypeptides of the Invention

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418, glutamine synthase, or neomycin resistance for eukaryotic cell culture, and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal

cells, such as yeast cells (e.g., Saccharomyces cerevisiae or Pichia pastoris (ATCC Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availabilty of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657, which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are herein incorporated by reference.

The present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have

characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., the coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., US Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller *et al., Proc. Natl. Acad. Sci. USA 86*:8932-8935 (1989); and Zijlstra *et al., Nature 342*:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

Polypeptides of the invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal

methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O_2. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O_2. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See Ellis, S.B., *et al., Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J, *et al., Yeast* 5:167-77 (1989); Tschopp, J.F., *et al., Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of

N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine (^{121}I, ^{123}I, ^{125}I, ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{111}In, ^{112}In, ^{113m}In, ^{115m}In), technetium (^{99}Tc,^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, and ^{97}Ru.

In specific embodiments, a polypeptide of the present invention or fragment or variant thereof is attached to macrocyclic chelators that associate with radiometal ions, including but not limited to, ^{177}Lu, ^{90}Y, ^{166}Ho, and ^{153}Sm, to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is ^{111}In. In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is ^{90}Y. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

As mentioned, the proteins of the invention may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Polypeptides of the invention may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine,

formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al., Appl. Biochem. Biotechnol. 56*:59-72 (1996); Vorobjev *et al., Nucleosides Nucleotides 18*:2745-2750 (1999); and Caliceti *et al., Bioconjug. Chem. 10*:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a

number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik et al., Exp. Hematol. 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No.

5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

The polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer refers to a multimer containing only polypeptides corresponding to a protein of the invention (e.g., the amino acid sequence of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X or the complement of SEQ ID NO:X, the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or an amino acid sequence encoded by cDNA contained in ATCC Deposit No:Z (including fragments, variants, splice variants, and fusion proteins, corresponding to these as described herein)). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing two polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing three polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked by, for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide

sequence (e.g., that recited in SEQ ID NO:Y, encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or encoded by the cDNA contained in ATCC Deposit No:Z). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of the invention (e.g., a polypeptide or fragment or variant of the amino acid sequence of SEQ ID NO:Y or a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or an epitope, of the present invention) as determined by immunoassays well known in the art for assaying specific antibody-antigen binding. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularly-made antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793;

Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues, or listed in the Tables and Figures. Preferred epitopes of the invention include the predicted epitopes shown in column 7 of Table 1B.1, as well as polynucleotides that encode these epitopes. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or Kd less than $5 X 10^{-2}$ M, 10^{-2} M, $5 X 10^{-3}$ M, 10^{-3} M, $5 X 10^{-4}$ M, 10^{-4} M, $5 X 10^{-5}$ M, 10^{-5} M, $5 X 10^{-6}$ M, 10^{-6}M, $5 X 10^{-7}$ M, 10^{7} M, $5 X 10^{-8}$ M, 10^{-8} M, $5 X 10^{-9}$ M, 10^{-9} M, $5 X 10^{-10}$ M, 10^{-10} M, $5 X 10^{-11}$ M, 10^{-11} M, $5 X 10^{-12}$ M, 10^{-12} M, $5 X 10^{-13}$ M, 10^{-13} M, $5 X 10^{-14}$ M, 10^{-14} M, $5 X 10^{-15}$ M, or 10^{-15} M.

The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments,

the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

Antibodies of the present invention may be used, for example, to purify, detect, and target the polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic and

therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety.

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387; the disclosures of which are incorporated herein by reference in their entireties.

The antibodies of the invention include derivatives that are modified, i.e, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of- interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A

Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of Current Protocols in Immunology, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

In general, the sample containing human B cells is innoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4

week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g, SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including *in vivo* use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage

display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181; and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" polypeptides of the invention using techniques well known

to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby block its biological activity. Alternatively, antibodies which bind to and enhance polypeptide multimerization and/or binding, and/or receptor/ligand multimerization, binding and/or signaling can be used to generate anti-idiotypes that function as agonists of a polypeptide of the invention and/or its ligand/receptor. Such agonistic anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens as agonists of the polypeptides of the invention or its ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby promote or enhance its biological activity.

Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., Hum. Gene Ther. 5:595-601 (1994); Marasco, W.A., Gene Ther. 4:11-15 (1997); Rondon and Marasco, Annu. Rev. Microbiol. 51:257-283 (1997); Proba et al., J. Mol. Biol. 275:245-253 (1998); Cohen et al., Oncogene 17:2445-2456 (1998); Ohage and Steipe, J. Mol. Biol. 291:1119-1128 (1999); Ohage et al., J. Mol. Biol. 291:1129-1134 (1999); Wirtz and Steipe, Protein Sci. 8:2245-2250 (1999); Zhu et al., J. Immunol. Methods 231:207-222 (1999); and references cited therein.

Polynucleotides Encoding Antibodies

The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y, to a polypeptide encoded by a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or to a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)),

which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described *supra*. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region

cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described *supra*, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Methods of Producing Antibodies

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. Methods of producing antibodies include, but are not limited to, hybridoma technology, EBV transformation, and other methods discussed herein as well as through the use recombinant DNA technology, as discussed below.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and *in vivo*

genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or *in vivo* recombination. Insertion in a non- essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired.

Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215 (1993)); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired

recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availabilty of cell lines (e.g., the murine myeloma cell line, NSO) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g. Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suplliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are incorporated in their entirities by reference herein.

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or *in vivo*, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., *supra*, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452 (1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J.

Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337- 11341 (1992) (said references incorporated by reference in their entireties).

As discussed, *supra*, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the *in vivo* half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See EP 394,827; and Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. See, for example, Fountoulakis et al., J. Biochem. 270:3958-3964 (1995). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. See, for example, EP A 232,262. Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995)).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials,

radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include 125I, 131I, 111In or 99Tc.

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, a-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol.*, *6*:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological

response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Immunophenotyping

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. Translation products of the gene of the present invention may be useful as cell-specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al., Cell, 96*:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic

patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a

secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., 32P or 125I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

Antibodies of the invention may be characterized using immunocytochemisty methods on cells (e.g., mammalian cells, such as CHO cells) transfected with a vector enabling the expression of an antigen or with vector alone using techniques commonly known in the art. Antibodies that bind antigen transfected cells, but not vector-only transfected cells, are antigen specific.

Therapeutic Uses

Table 1D also provides information regarding biological activities and preferred therapeutic uses (i.e. see, "Preferred Indications" column) for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table 1D also provides information regarding assays which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("cDNA ATCC Deposit No:Z") provides the unique clone identifier for each clone as previously described and indicated in Table 1A, Table 1B, and Table 1C. The third column ("AA SEQ ID NO:Y") indicates the Sequence Listing SEQ ID Number for polypeptide sequences encoded by the corresponding cDNA clones (also as indicated in Table 1A, Table 1B, and Table 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides (or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and also provides information pertaining to the various types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity.

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, gastrointestinal diseases and disorders. The treatment and/or prevention of gastrointestinal diseases and disorders associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with gastrointestinal diseases and disorders. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating gastrointestinal diseases and disorders. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a polypeptide of the invention (such as, for example, a predicted linear epitope shown in column 7 of Table 1B.1; or a conformational epitope,

including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to detect, diagnose, prevent, treat, prognosticate, and/or ameliorate gastrointestinal diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention. The treatment and/or prevention of gastrointestinal diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of gastrointestinal diseases and disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

Gene Therapy

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a gastrointestinal disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

In a preferred embodiment, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic

acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al.,

Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143- 155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor

cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by the presence or absence of an appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Activity

The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other

vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic

aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, prognosticate, or monitor gastrointestinal diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a gastrointestinal disease or disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular gastrointestional disease or disorder. With respect to gastrointestinal cancers, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the gastrointestinal cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval

following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with

specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface- bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art. Table 1B.1, column 8 provides the chromosome location of some of the polynucleotides of the invention.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal

cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 1B and/or Table 2 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library)). Column 9 of Table 1B.1 provides an OMIM reference identification number of diseases associated with the cytologic band disclosed in column 8 of Table 1B.1, as determined using techniques described herein and by reference to Table 5. Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined

in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker. Diagnostic and prognostic methods, kits and reagents encompassed by the present invention are briefly described below and more thoroughly elsewhere herein (see e.g., the sections labeled "Antibodies", "Diagnostic Assays", and "Methods for Detecting Diseases").

Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder. Additional non-limiting examples of diagnostic methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., Example 12).

In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of polynucleotides of the invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or

relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the related disorder or being determined by averaging levels from a population of individuals not having a related disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains polypeptide of the present invention or the corresponding mRNA. As indicated, biological samples include body fluids (such as semen, lymph, vaginal pool, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the invention attached may be used to identify polymorphisms between the isolated polynucleotide sequences of the invention, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, digestive disorders, metabolic disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced *supra* are hereby incorporated by reference in their entirety herein.

The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by Nielsen et al., Science 254, 1497 (1991); and Egholm et al., Nature 365, 666 (1993), PNAs bind

specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T.sub.m) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The compounds of the present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Gelmann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelmann et al., *supra*) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., *supra*) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., *supra*)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc.

Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not be limited to treatment, prevention, and/or prognosis of proliferative disorders of cells and tissues of hematopoietic origin, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

In addition to the foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions. Non-limiting antisense and triple helix methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the section labeled "Antisense and Ribozyme (Antagonists)").

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy Methods", and Examples 16, 17 and 18).

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's

genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992)). Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers prepared from the sequences of the present invention, specific to tissues, including but not limited to those shown in Table 1B. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination. Additional non-limiting examples of such uses are further described herein.

The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, for example, those

disclosed in Table 1B, and/or cancerous and/or wounded tissues) or bodily fluids (e.g., semen, lymph, vaginal pool, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected *in vivo* by imaging. Antibody labels or markers for *in vivo*

imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc, (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F, ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for

example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi, or other radioisotopes such as, for example, ^{103}Pd, ^{133}Xe, ^{131}I, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{35}S, ^{90}Y, ^{153}Sm, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{90}Yttrium, ^{117}Tin, ^{186}Rhenium, ^{166}Holmium, and ^{188}Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{90}Y. In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{111}In. In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{131}I.

Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Moreover, polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example,

patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the biological activities described herein.

Diagnostic Assays

The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, those related to biological activities described in Table 1D and, also as described herein under the section heading "Biological Activities".

For a number of disorders, substantially altered (increased or decreased) levels of gene expression can be detected in tissues, cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, that is, the expression level in tissues or bodily fluids from an individual not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a disorder, which involves measuring the expression level of the gene encoding the polypeptide in tissues, cells or body fluid from an individual and comparing the measured gene expression level with a standard gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue.

The present invention is also useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognosticate diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B.2, column 5 (Tissue Distribution Library Code).

By "assaying the expression level of the gene encoding the polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having the disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing polypeptides of the invention (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) and tissue sources found to express the full length or fragments thereof of a polypeptide or mRNA. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, Anal. Biochem. 162:156-159 (1987). Levels of mRNA encoding the polypeptides of the invention are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of polypeptides of the invention, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of

polypeptides of the invention compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as a polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying polypeptide levels in a biological sample can occur using any art-known method.

Assaying polypeptide levels in a biological sample can occur using antibody-based techniques. For example, polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99m}Tc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the gene of inteest (such as, for example, cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the gene.

For example, antibodies, or fragments of antibodies, such as those described herein, may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the polypeptides of the invention (shown in column 7 of Table 1B.1) may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of a polypeptide of the invention may be used to quantitatively or

qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

The antibodies (or fragments thereof), and/or polypeptides of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of gene products or conserved variants or peptide fragments thereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or polypeptide of the present invention. The antibody (or fragment thereof) or polypeptide is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the gene product, or conserved variants or peptide fragments, or polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

Immunoassays and non-immunoassays for gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled antibody or detectable polypeptide of the invention. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such

as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

The binding activity of a given lot of antibody or antigen polypeptide may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

In addition to assaying polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, polypeptide or polynucleotide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, polypeptides and/or antibodies of the invention are used to image diseased cells, such as neoplasms. In another embodiment, polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of an mRNA) and/or antibodies (e.g., antibodies directed to any one or a combination of the epitopes of a polypeptide of the invention, antibodies directed to a conformational epitope of a polypeptide of the invention, or antibodies directed to the full length polypeptide expressed on the cell surface of a mammalian cell) are used to image diseased or neoplastic cells.

Antibody labels or markers for *in vivo* imaging of polypeptides of the invention include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where *in vivo* imaging is used to detect enhanced levels of polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using techniques described herein or otherwise known in the art. For example methods for producing chimeric antibodies are known in the art. See, for review, Morrison, *Science 229*:1202 (1985); Oi et al., *BioTechniques 4*:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne *et al., Nature 312*:643 (1984); Neuberger *et al., Nature 314*:268 (1985).

Additionally, any polypeptides of the invention whose presence can be detected, can be administered. For example, polypeptides of the invention labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further, such polypeptides can be utilized for *in vitro* diagnostic procedures.

A polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a disorder. It will be understood in the art that the size of the subject and the imaging system used

will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the antigenic protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

With respect to antibodies, one of the ways in which an antibody of the present invention can be detectably labeled is by linking the same to a reporter enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL,; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kgaku Shoin, Tokyo). The reporter enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Reporter enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the reporter enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect polypeptides through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

The antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Methods for Detecting Diseases

In general, a disease may be detected in a patient based on the presence of one or more proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a disease or disorder, including cancer and/or as described elsewhere herein. In addition, such proteins may be useful for the detection of other diseases and cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding polypeptides of the invention, which is also indicative of the presence or absence of a disease or disorder, including cancer. In general, polypeptides of the invention should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *supra*. In general, the presence or absence of a disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of a binding agent(s) immobilized on a solid support to bind to and remove the polypeptide of the invention from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection

reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include polypeptides of the invention and portions thereof, or antibodies, to which the binding agent binds, as described above.

The solid support may be any material known to those of skill in the art to which polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 ug, and preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

Gene Therapy Methods

Also encompassed by the invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and

pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such

materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+}-EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394:483; Wilson et al., Cell 17:77 (1979)); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka, F. and

Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA 75:145 (1978); Schaefer-Ridder et al., Science 215:166 (1982)), which are herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, ex vivo or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and $CaPO_4$ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or *in vivo*. The transduced eukaryotic cells will express a polypeptide of the present invention.

In certain other embodiments, cells are engineered, ex vivo or *in vivo*, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for

many years with an excellent safety profile (Schwartz et al. Am. Rev. Respir. Dis.109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the El region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, ex vivo or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected

and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), which are herein encorporated by reference. This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

The polynucleotide encoding a polypeptide of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising polypeptides of the invention for targeting the vehicle to a particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive

enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

Biological Activities

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

Members of the secreted family of proteins are believed to be involved in biological activities associated with, for example, cellular signaling. Accordingly, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders associated with aberrant activity of secreted polypeptides.

In preferred embodiments, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in the diagnosis, prognosis, prevention, treatment, and/or amelioration of diseases and/or disorders relating to the gastrointestinal system (e.g., Crohn's disease, pancreatitis, gallstones, antibiotic-associated colitis, duodenitis, gastrointestinal neoplasms, and as described in the "Gastrointestinal Disorders" section below). In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognosticate diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed including one, two, three, four, five, or more tissues disclosed in Table 1B.2, column 5 (Tissue Distribution Library Code).

Thus, polynucleotides, translation products and antibodies of the invention are useful in the diagnosis, detection, prevention, prognistication, and/or treatment of diseases and/or disorders associated with activities that include, but are not limited to, prohormone activation, neurotransmitter activity, cellular signaling, cellular proliferation, cellular differentiation, and cell migration.

More generally, polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, treatment and/or amelioration of diseases and/or disorders associated with the following system or systems.

<u>Immune Activity</u>

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, prognosticating, treating, and/or ameliorating diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

<u>Wound Healing and Epithelial Cell Proliferation</u>

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or

antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat

gastric and doudenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Gastrointestinal Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate gastrointestinal diseases and disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowl lymphoma)), and ulcers, such as peptic ulcers.

Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperioneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess,).

Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata, Echinococcus granulosus, Diphyllobothrium spp.*, and *T. solium*).

Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms

(angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Karposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoin neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-

obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowl syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

Chemotaxis

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial

cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors),or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures.

The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labeled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al., Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al., J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be

achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and ^{3}[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of ^{3}[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of ^{3}[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured

to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause

the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Antisense And Ribozyme (Antagonists)

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to cDNA sequences contained in cDNA ATCC Deposit No:Z identified for example, in Table 1A and/or 1B. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for *in vivo* use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5 end and a HindIII site on the 3 end. Next, the pair of oligonucleotides is

heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl2, 10MM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, et al., Nature 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently

at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-

carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g., for improved stability, targeting, etc.) and should be delivered to cells

which express *in vivo*. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

The antagonist/agonist may also be employed to treat the diseases described herein.

Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

Binding Peptides and Other Molecules

The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

This method comprises the steps of:

contacting polypeptides of the invention with a plurality of molecules; and

identifying a molecule that binds the polypeptides of the invention.

The step of contacting the polypeptides of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the polypeptides on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptides. Such a procedure would be akin to an affinity

chromatographic process, with the affinity matrix being comprised of the immobilized polypeptides of the invention. The molecules having a selective affinity for the polypeptides can then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptides to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by the polypeptides of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptides and the individual clone. Prior to contacting the polypeptides with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for polypeptides of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptides of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

In certain situations, it may be desirable to wash away any unbound polypeptides from a mixture of the polypeptides of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the polypeptides of the invention or the plurality of polypeptides are bound to a solid support.

The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind polypeptides of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; Medynski, 1994, Bio/Technology 12:709-

710;Gallop et al., 1994, J. Medicinal Chemistry 37(9):1233-1251; Ohlmeyer et al., 1993, Proc. Natl. Acad. Sci. USA 90:10922-10926; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422-11426; Houghten et al., 1992, Biotechniques 13:412; Jayawickreme et al., 1994, Proc. Natl. Acad. Sci. USA 91:1614-1618; Salmon et al., 1993, Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383.

Examples of phage display libraries are described in Scott and Smith, 1990, Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718); Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known

methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992; BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al., 1994, Cell 76:933-945; Staudt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds polypeptides of the invention can be carried out by contacting the library members with polypeptides of the invention immobilized on a solid phase and harvesting those library members that bind to the polypeptides of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to polypeptides of the invention.

Where the binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

As mentioned above, in the case of a binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

The selected binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Other Activities

A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be

used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in Table 1B or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC Deposit No:Z.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of the portion of SEQ ID NO:X as defined in column 5, "ORF (From-To)", in Table 1B.1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of the portion of SEQ ID NO:X as defined in columns 8 and 9, "NT From" and "NT To" respectively, in Table 2.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in Table 1B or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC Deposit No:Z.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide

sequence as defined in Table 1B or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC Deposit No:Z.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of the portion of SEQ ID NO:X defined in column 5, "ORF (From-To)", in Table 1B.1.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of the portion of SEQ ID NO:X defined in columns 8 and 9, "NT From" and "NT To", respectively, in Table 2.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC Deposit No:Z, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises the cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides of the cDNA sequence contained in ATCC Deposit No:Z.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by cDNA contained in ATCC Deposit No:Z.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by cDNA contained in ATCC Deposit No:Z.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by cDNA contained in ATCC Deposit No:Z.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence encoded by cDNA contained in ATCC Deposit No:Z; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence of the cDNA contained in ATCC Deposit No:Z.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; or the cDNA contained in ATCC Deposit No:Z which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of

Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence of cDNA contained in ATCC Deposit No:Z.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence encoded by cDNA contained in ATCC Deposit No:Z. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000, or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A and/or 1B; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA "Clone ID" in Table 1A and/or 1B.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCC Deposit No:Z.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCC Deposit No:Z.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCC Deposit No:Z.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by contained in ATCC Deposit No:Z

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded by cDNA contained in ATCC Deposit No:Z; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or the polypeptide sequence of SEQ ID NO:Y.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a polypeptide encoded by cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the

sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1A, 1B or Table 2 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is a polypeptide molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a specific delivery of toxic compositions to diseased cells (e.g., tumors, leukemias or lymphomas), which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide of the invention, including, but not limited to a binding agent, or antibody of the claimed invention that are associated with toxin or cytotoxic prodrugs.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Description of Table 6

Table 6 summarizes some of the ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application. These deposits were made in addition to those described in the Table 1A.

Table 6

ATCC Deposits	Deposit Date	ATCC Designation Number
LP01, LP02, LP03, LP04, LP05, LP06, LP07, LP08, LP09, LP10, LP11,	May-20-97	209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069
LP12	Jan-12-98	209579
LP13	Jan-12-98	209578
LP14	Jul-16-98	203067
LP15	Jul-16-98	203068
LP16	Feb-1-99	203609
LP17	Feb-1-99	203610
LP20	Nov-17-98	203485
LP21	Jun-18-99	PTA-252
LP22	Jun-18-99	PTA-253
LP23	Dec-22-99	PTA-1081

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each ATCC Deposit No:Z is contained in a plasmid vector. Table 7 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The following correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 7 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

Vector Used to Construct Library	Corresponding Deposited Plasmid
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSport 2.0	pCMVSport 2.0
pCMVSport 3.0	pCMVSport 3.0
pCR®2.1	pCR®2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993)). Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be

transformed into E. coli strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991)). Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 7, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited by reference to Table 1A, Table 2, Table 6 and Table 7 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each ATCC Deposit No:Z.

TABLE 7

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HUKA HUKB HUKC HUKD HUKE HUKF HUKG	Human Uterine Cancer	Lambda ZAP II	LP01
HCNA HCNB	Human Colon	Lambda Zap II	LP01
HFFA	Human Fetal Brain, random primed	Lambda Zap II	LP01
HTWA	Resting T-Cell	Lambda ZAP II	LP01
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP01
HLMB HLMF HLMG HLMH HLMI HLMJ HLMM HLMN	breast lymph node CDNA library	Lambda ZAP II	LP01
HCQA HCQB	human colon cancer	Lamda ZAP II	LP01
HMEA HMEC HMED HMEE HMEF HMEG HMEI HMEJ HMEK HMEL	Human Microvascular Endothelial Cells, fract. A	Lambda ZAP II	LP01
HUSA HUSC	Human Umbilical Vein Endothelial Cells, fract. A	Lambda ZAP II	LP01
HLQA HLQB	Hepatocellular Tumor	Lambda ZAP II	LP01
HHGA HHGB HHGC HHGD	Hemangiopericytoma	Lambda ZAP II	LP01
HSDM	Human Striatum Depression, re-rescue	Lambda ZAP II	LP01
HUSH	H Umbilical Vein Endothelial Cells, frac A, re-excision	Lambda ZAP II	LP01
HSGS	Salivary gland, subtracted	Lambda ZAP II	LP01
HFXA HFXB HFXC HFXD HFXE HFXF HFXG HFXH	Brain frontal cortex	Lambda ZAP II	LP01
HPQA HPQB HPQC	PERM TF274	Lambda ZAP II	LP01
HFXJ HFXK	Brain Frontal Cortex, re-excision	Lambda ZAP II	LP01
HCWA HCWB HCWC HCWD HCWE HCWF HCWG HCWH HCWI HCWJ HCWK	CD34 positive cells (Cord Blood)	ZAP Express	LP02
HCUA HCUB HCUC	CD34 depleted Buffy Coat	ZAP Express	LP02

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	(Cord Blood)		
HRSM	A-14 cell line	ZAP Express	LP02
HRSA	A1-CELL LINE	ZAP Express	LP02
HCUD HCUE HCUF HCUG HCUH HCUI	CD34 depleted Buffy Coat (Cord Blood), re-excision	ZAP Express	LP02
HBXE HBXF HBXG	H. Whole Brain #2, re-excision	ZAP Express	LP02
HRLM	L8 cell line	ZAP Express	LP02
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP02
HUDA HUDB HUDC	Testes	ZAP Express	LP02
HHTM HHTN HHTO	H. hypothalamus, frac A;re-excision	ZAP Express	LP02
HHTL	H. hypothalamus, frac A	ZAP Express	LP02
HASA HASD	Human Adult Spleen	Uni-ZAP XR	LP03
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP03
HE8A HE8B HE8C HE8D HE8E HE8F HE8M HE8N	Human 8 Week Whole Embryo	Uni-ZAP XR	LP03
HGBA HGBD HGBE HGBF HGBG HGBH HGBI	Human Gall Bladder	Uni-ZAP XR	LP03
HLHA HLHB HLHC HLHD HLHE HLHF HLHG HLHH HLHQ	Human Fetal Lung III	Uni-ZAP XR	LP03
HPMA HPMB HPMC HPMD HPME HPMF HPMG HPMH	Human Placenta	Uni-ZAP XR	LP03
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP03
HSIA HSIC HSID HSIE	Human Adult Small Intestine	Uni-ZAP XR.	LP03
HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEI HTEJ HTEK	Human Testes	Uni-ZAP XR	LP03
HTPA HTPB HTPC HTPD HTPE	Human Pancreas Tumor	Uni-ZAP XR	LP03
HTTA HTTB HTTC HTTD HTTE HTTF	Human Testes Tumor	Uni-ZAP XR	LP03
HAPA HAPB HAPC HAPM	Human Adult Pulmonary	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETE HETF HETG HETH HETI	Human Endometrial Tumor	Uni-ZAP XR	LP03
HHFB HHFC HHFD HHFE HHFF HHFG HHFH HHFI	Human Fetal Heart	Uni-ZAP XR	LP03
HHPB HHPC HHPD HHPE HHPF HHPG HHPH	Human Hippocampus	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCE5 HCEB HCEC HCED HCEE HCEF HCEG	Human Cerebellum	Uni-ZAP XR	LP03
HUVB HUVC HUVD HUVE	Human Umbilical Vein, Endo. remake	Uni-ZAP XR	LP03
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP03
HTAA HTAB HTAC HTAD HTAE	Human Activated T-Cells	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HFEA HFEB HFEC	Human Fetal Epithelium (Skin)	Uni-ZAP XR	LP03
HJPA HJPB HJPC HJPD	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Uni-ZAP XR	LP03
HESA	Human epithelioid sarcoma	Uni-Zap XR	LP03
HLTA HLTB HLTC HLTD HLTE HLTF	Human T-Cell Lymphoma	Uni-ZAP XR	LP03
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP03
HRDA HRDB HRDC HRDD HRDE HRDF	Human Rhabdomyosarcoma	Uni-ZAP XR	LP03
HCAA HCAB HCAC	Cem cells cyclohexamide treated	Uni-ZAP XR	LP03
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HSUA HSUB HSUC HSUM	Supt Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HT4A HT4C HT4D	Activated T-Cells, 12 hrs.	Uni-ZAP XR	LP03
HE9A HE9B HE9C HE9D HE9E HE9F HE9G HE9H HE9M HE9N	Nine Week Old Early Stage Human	Uni-ZAP XR	LP03
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP03
HT5A	Activated T-Cells, 24 hrs.	Uni-ZAP XR	LP03
HFGA HFGM	Human Fetal Brain	Uni-ZAP XR	LP03
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP03
HBGB HBGD	Human Primary Breast Cancer	Uni-ZAP XR	LP03
HBNA HBNB	Human Normal Breast	Uni-ZAP XR	LP03
HCAS	Cem Cells, cyclohexamide treated, subtra	Uni-ZAP XR	LP03
HHPS	Human Hippocampus, subtracted	pBS	LP03
HKCS HKCU	Human Colon Cancer, subtracted	pBS	LP03
HRGS	Raji cells, cyclohexamide treated, subtracted	pBS	LP03
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBS	LP03
HT4S	Activated T-Cells, 12 hrs, subtracted	Uni-ZAP XR	LP03
HCDA HCDB HCDC HCDD HCDE	Human Chondrosarcoma	Uni-ZAP XR	LP03
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP03
HTLA HTLB HTLC HTLD HTLE HTLF	Human adult testis, large inserts	Uni-ZAP XR	LP03
HLMA HLMC HLMD	Breast Lymph node cDNA library	Uni-ZAP XR	LP03
H6EA H6EB H6EC	HL-60, PMA 4H	Uni-ZAP XR	LP03
HTXA HTXB HTXC HTXD HTXE HTXF HTXG HTXH	Activated T-Cell (12hs)/Thiouridine labelledEco	Uni-ZAP XR	LP03
HNFA HNFB HNFC HNFD	Human Neutrophil, Activated	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HNFE HNFF HNFG HNFH HNFJ			
HTOB HTOC	HUMAN TONSILS, FRACTION 2	Uni-ZAP XR	LP03
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP03
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP03
HORB	Human OB HOS treated (10 nM E2) fraction I	Uni-ZAP XR	LP03
HSVA HSVB HSVC	Human Chronic Synovitis	Uni-ZAP XR	LP03
HROA	HUMAN STOMACH	Uni-ZAP XR	LP03
HBJA HBJB HBJC HBJD HBJE HBJF HBJG HBJH HBJI HBJJ HBJK	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP03
HCRA HCRB HCRC	human corpus colosum	Uni-ZAP XR	LP03
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP03
HDSA	Dermatofibrosarcoma Protuberance	Uni-ZAP XR	LP03
HMWA HMWB HMWC HMWD HMWE HMWF HMWG HMWH HMWI HMWJ	Bone Marrow Cell Line (RS4;11)	Uni-ZAP XR	LP03
HSOA	stomach cancer (human)	Uni-ZAP XR	LP03
HERA	SKIN	Uni-ZAP XR	LP03
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP03
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP03
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP03
HBCA HBCB	H. Lymph node breast Cancer	Uni-ZAP XR	LP03
HPWT	Human Prostate BPH, re-excision	Uni-ZAP XR	LP03
HFVG HFVH HFVI	Fetal Liver, subtraction II	pBS	LP03
HNFI	Human Neutrophils, Activated, re-excision	pBS	LP03
HBMB HBMC HBMD	Human Bone Marrow, re-excision	pBS	LP03
HKML HKMM HKMN	H. Kidney Medulla, re-excision	pBS	LP03
HKIX HKIY	H. Kidney Cortex, subtracted	pBS	LP03
HADT	H. Amygdala Depression, subtracted	pBS	LP03
H6AS	Hl-60, untreated, subtracted	Uni-ZAP XR	LP03
H6ES	HL-60, PMA 4H, subtracted	Uni-ZAP XR	LP03
H6BS	HL-60, RA 4h, Subtracted	Uni-ZAP XR	LP03
H6CS	HL-60, PMA 1d, subtracted	Uni-ZAP XR	LP03
HTXJ HTXK	Activated T-cell(12h)/Thiouridine-re-excision	Uni-ZAP XR	LP03
HMSA HMSB HMSC HMSD HMSE HMSF HMSG HMSH HMSI HMSJ HMSK	Monocyte activated	Uni-ZAP XR	LP03
HAGA HAGB HAGC HAGD	Human Amygdala	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HAGE HAGF			
HSRA HSRB HSRE	STROMAL - OSTEOCLASTOMA	Uni-ZAP XR	LP03
HSRD HSRF HSRG HSRH	Human Osteoclastoma Stromal Cells - unamplified	Uni-ZAP XR	LP03
HSQA HSQB HSQC HSQD HSQE HSQF HSQG	Stromal cell TF274	Uni-ZAP XR	LP03
HSKA HSKB HSKC HSKD HSKE HSKF HSKZ	Smooth muscle, serum treated	Uni-ZAP XR	LP03
HSLA HSLB HSLC HSLD HSLE HSLF HSLG	Smooth muscle,control	Uni-ZAP XR	LP03
HSDA HSDD HSDE HSDF HSDG HSDH	Spinal cord	Uni-ZAP XR	LP03
HPWS	Prostate-BPH subtracted II	pBS	LP03
HSKW HSKX HSKY	Smooth Muscle- HASTE normalized	pBS	LP03
HFPB HFPC HFPD	H. Frontal cortex,epileptic;re-excision	Uni-ZAP XR	LP03
HSDI HSDJ HSDK	Spinal Cord, re-excision	Uni-ZAP XR	LP03
HSKN HSKO	Smooth Muscle Serum Treated, Norm	pBS	LP03
HSKG HSKH HSKI	Smooth muscle, serum induced,re-exc	pBS	LP03
HFCA HFCB HFCC HFCD HFCE HFCF	Human Fetal Brain	Uni-ZAP XR	LP04
HPTA HPTB HPTD	Human Pituitary	Uni-ZAP XR	LP04
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP04
HE6B HE6C HE6D HE6E HE6F HE6G HE6S	Human Whole Six Week Old Embryo	Uni-ZAP XR	LP04
HSSA HSSB HSSC HSSD HSSE HSSF HSSG HSSH HSSI HSSJ HSSK	Human Synovial Sarcoma	Uni-ZAP XR	LP04
HE7T	7 Week Old Early Stage Human, subtracted	Uni-ZAP XR	LP04
HEPA HEPB HEPC	Human Epididymus	Uni-ZAP XR	LP04
HSNA HSNB HSNC HSNM HSNN	Human Synovium	Uni-ZAP XR	LP04
HPFB HPFC HPFD HPFE	Human Prostate Cancer, Stage C fraction	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2M HE2N HE2O	12 Week Old Early Stage Human	Uni-ZAP XR	LP04
HE2B HE2C HE2F HE2G HE2P HE2Q	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP04
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP04
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP04
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP04
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP04
HBSD	Bone Cancer, re-excision	Uni-ZAP XR	LP04
HSGB	Salivary gland, re-excision	Uni-ZAP XR	LP04

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP04
HSXA HSXB HSXC HSXD	Human Substantia Nigra	Uni-ZAP XR	LP04
HSHA HSHB HSHC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP04
HOUA HOUB HOUC HOUD HOUE	Adipocytes	Uni-ZAP XR	LP04
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP04
HELA HELB HELC HELD HELE HELF HELG HELH	Endothelial cells-control	Uni-ZAP XR	LP04
HEMA HEMB HEMC HEMD HEME HEMF HEMG HEMH	Endothelial-induced	Uni-ZAP XR	LP04
HBIA HBIB HBIC	Human Brain, Striatum	Uni-ZAP XR	LP04
HHSA HHSB HHSC HHSD HHSE	Human Hypothalmus,Schizophrenia	Uni-ZAP XR	LP04
HNGA HNGB HNGC HNGD HNGE HNGF HNGG HNGH HNGI HNGJ	neutrophils control	Uni-ZAP XR	LP04
HNHA HNHB HNHC HNHD HNHE HNHF HNHG HNHH HNHI HNHJ	Neutrophils IL-1 and LPS induced	Uni-ZAP XR	LP04
HSDB HSDC	STRIATUM DEPRESSION	Uni-ZAP XR	LP04
HHPT	Hypothalamus	Uni-ZAP XR	LP04
HSAT HSAU HSAV HSAW HSAX HSAY HSAZ	Anergic T-cell	Uni-ZAP XR	LP04
HBMS HBMT HBMU HBMV HBMW HBMX	Bone marrow	Uni-ZAP XR	LP04
HOEA HOEB HOEC HOED HOEE HOEF HOEJ	Osteoblasts	Uni-ZAP XR	LP04
HAIA HAIB HAIC HAID HAIE HAIF	Epithelial-TNFa and INF induced	Uni-ZAP XR	LP04
HTGA HTGB HTGC HTGD	Apoptotic T-cell	Uni-ZAP XR	LP04
HMCA HMCB HMCC HMCD HMCE	Macrophage-oxLDL	Uni-ZAP XR	LP04
HMAA HMAB HMAC HMAD HMAE HMAF HMAG	Macrophage (GM-CSF treated)	Uni-ZAP XR	LP04
HPHA	Normal Prostate	Uni-ZAP XR	LP04
HPIA HPIB HPIC	LNCAP prostate cell line	Uni-ZAP XR	LP04
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP04
HOSE HOSF HOSG	Human Osteoclastoma, re-excision	Uni-ZAP XR	LP04
HTGE HTGF	Apoptotic T-cell, re-excision	Uni-ZAP XR	LP04
HMAJ HMAK	H Macrophage (GM-CSF treated), re-excision	Uni-ZAP XR	LP04
HACB HACC HACD	Human Adipose Tissue, re-excision	Uni-ZAP XR	LP04
HFPA	H. Frontal Cortex, Epileptic	Uni-ZAP XR	LP04
HFAA HFAB HFAC HFAD HFAE	Alzheimer's, spongy change	Uni-ZAP XR	LP04
HFAM	Frontal Lobe, Dementia	Uni-ZAP XR	LP04
HMIA HMIB HMIC	Human Manic Depression	Uni-ZAP XR	LP04

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	Tissue		
HTSA HTSE HTSF HTSG HTSH	Human Thymus	pBS	LP05
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBS	LP05
HSAA HSAB HSAC	HSA 172 Cells	pBS	LP05
HSBA HSBB HSBC HSBM	HSC172 cells	pBS	LP05
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBS	LP05
HJBA HJBB HJBC HJBD	Jurkat T-Cell, S phase	pBS	LP05
HAFA HAFB	Aorta endothelial cells + TNF-a	pBS	LP05
HAWA HAWB HAWC	Human White Adipose	pBS	LP05
HTNA HTNB	Human Thyroid	pBS	LP05
HONA	Normal Ovary, Premenopausal	pBS	LP05
HARA HARB	Human Adult Retina	pBS	LP05
HLJA HLJB	Human Lung	pCMVSport 1	LP06
HOFM HOFN HOFO	H. Ovarian Tumor, II, OV5232	pCMVSport 2.0	LP07
HOGA HOGB HOGC	OV 10-3-95	pCMVSport 2.0	LP07
HCGL	CD34+cells, II	pCMVSport 2.0	LP07
HDLA	Hodgkin's Lymphoma I	pCMVSport 2.0	LP07
HDTA HDTB HDTC HDTD HDTE	Hodgkin's Lymphoma II	pCMVSport 2.0	LP07
HKAA HKAB HKAC HKAD HKAE HKAF HKAG HKAH	Keratinocyte	pCMVSport2.0	LP07
HCIM	CAPFINDER, Crohn's Disease, lib 2	pCMVSport 2.0	LP07
HKAL	Keratinocyte, lib 2	pCMVSport2.0	LP07
HKAT	Keratinocyte, lib 3	pCMVSport2.0	LP07
HNDA	Nasal polyps	pCMVSport2.0	LP07
HDRA	H. Primary Dendritic Cells,lib 3	pCMVSport2.0	LP07
HOHA HOHB HOHC	Human Osteoblasts II	pCMVSport2.0	LP07
HLDA HLDB HLDC	Liver, Hepatoma	pCMVSport3.0	LP08
HLDN HLDO HLDP	Human Liver, normal	pCMVSport3.0	LP08
HMTA	pBMC stimulated w/ poly I/C	pCMVSport3.0	LP08
HNTA	NTERA2, control	pCMVSport3.0	LP08
HDPA HDPB HDPC HDPD HDPF HDPG HDPH HDPI HDPJ HDPK	Primary Dendritic Cells, lib 1	pCMVSport3.0	LP08
HDPM HDPN HDPO HDPP	Primary Dendritic cells,frac 2	pCMVSport3.0	LP08
HMUA HMUB HMUC	Myoloid Progenitor Cell Line	pCMVSport3.0	LP08
HHEA HHEB HHEC HHED	T Cell helper I	pCMVSport3.0	LP08
HHEM HHEN HHEO HHEP	T cell helper II	pCMVSport3.0	LP08
HEQA HEQB HEQC	Human endometrial stromal cells	pCMVSport3.0	LP08
HJMA HJMB	Human endometrial stromal cells-treated with progesterone	pCMVSport3.0	LP08
HSWA HSWB HSWC	Human endometrial stromal cells-treated with estradiol	pCMVSport3.0	LP08
HSYA HSYB HSYC	Human Thymus Stromal Cells	pCMVSport3.0	LP08
HLWA HLWB HLWC	Human Placenta	pCMVSport3.0	LP08
HRAA HRAB HRAC	Rejected Kidney, lib 4	pCMVSport3.0	LP08

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HMTM	PCR, pBMC I/C treated	PCRII	LP09
HMJA	H. Meniingima, M6	pSport 1	LP10
HMKA HMKB HMKC HMKD HMKE	H. Meningima, M1	pSport 1	LP10
HUSG HUSI	Human umbilical vein endothelial cells, IL-4 induced	pSport 1	LP10
HUSX HUSY	Human Umbilical Vein Endothelial Cells, uninduced	pSport 1	LP10
HOFA	Ovarian Tumor I, OV5232	pSport 1	LP10
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport 1	LP10
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport 1	LP10
HADA HADC HADD HADE HADF HADG	Human Adipose	pSport 1	LP10
HOVA HOVB HOVC	Human Ovary	pSport 1	LP10
HTWB HTWC HTWD HTWE HTWF	Resting T-Cell Library,II	pSport 1	LP10
HMMA	Spleen metastic melanoma	pSport 1	LP10
HLYA HLYB HLYC HLYD HLYE	Spleen, Chronic lymphocytic leukemia	pSport 1	LP10
HCGA	CD34+ cell, I	pSport 1	LP10
HEOM HEON	Human Eosinophils	pSport 1	LP10
HTDA	Human Tonsil, Lib 3	pSport 1	LP10
HSPA	Salivary Gland, Lib 2	pSport 1	LP10
HCHA HCHB HCHC	Breast Cancer cell line, MDA 36	pSport 1	LP10
HCHM HCHN	Breast Cancer Cell line, angiogenic	pSport 1	LP10
HCIA	Crohn's Disease	pSport 1	LP10
HDAA HDAB HDAC	HEL cell line	pSport 1	LP10
HABA	Human Astrocyte	pSport 1	LP10
HUFA HUFB HUFC	Ulcerative Colitis	pSport 1	LP10
HNTM	NTERA2 + retinoic acid, 14 days	pSport 1	LP10
HDQA	Primary Dendritic cells,CapFinder2, frac 1	pSport 1	LP10
HDQM	Primary Dendritic Cells, CapFinder, frac 2	pSport 1	LP10
HLDX	Human Liver, normal,CapFinder	pSport 1	LP10
HULA HULB HULC	Human Dermal Endothelial Cells,untreated	pSport1	LP10
HUMA	Human Dermal Endothelial cells,treated	pSport1	LP10
HCJA	Human Stromal Endometrial fibroblasts, untreated	pSport1	LP10
HCJM	Human Stromal endometrial fibroblasts, treated w/ estradiol	pSport1	LP10
HEDA	Human Stromal endometrial fibroblasts, treated with progesterone	pSport1	LP10
HFNA	Human ovary tumor cell OV350721	pSport1	LP10

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HKGA HKGB HKGC HKGD	Merkel Cells	pSport1	LP10
HISA HISB HISC	Pancreas Islet Cell Tumor	pSport1	LP10
HLSA	Skin, burned	pSport1	LP10
HBZA	Prostate,BPH, Lib 2	pSport 1	LP10
HBZS	Prostate BPH,Lib 2, subtracted	pSport 1	LP10
HFIA HFIB HFIC	Synovial Fibroblasts (control)	pSport 1	LP10
HFIH HFII HFIJ	Synovial hypoxia	pSport 1	LP10
HFIT HFIU HFIV	Synovial IL-1/TNF stimulated	pSport 1	LP10
HGCA	Messangial cell, frac 1	pSport1	LP10
HMVA HMVB HMVC	Bone Marrow Stromal Cell, untreated	pSport1	LP10
HFIX HFIY HFIZ	Synovial Fibroblasts (Il1/TNF), subt	pSport1	LP10
HFOX HFOY HFOZ	Synovial hypoxia-RSF subtracted	pSport1	LP10
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP11
HLIA HLIB HLIC	Human Liver	pCMVSport 1	LP012
HHBA HHBB HHBC HHBD HHBE	Human Heart	pCMVSport 1	LP012
HBBA HBBB	Human Brain	pCMVSport 1	LP012
HLJA HLJB HLJC HLJD HLJE	Human Lung	pCMVSport 1	LP012
HOGA HOGB HOGC	Ovarian Tumor	pCMVSport 2.0	LP012
HTJM	Human Tonsils, Lib 2	pCMVSport 2.0	LP012
HAMF HAMG	KMH2	pCMVSport 3.0	LP012
HAJA HAJB HAJC	L428	pCMVSport 3.0	LP012
HWBA HWBB HWBC HWBD HWBE	Dendritic cells, pooled	pCMVSport 3.0	LP012
HWAA HWAB HWAC HWAD HWAE	Human Bone Marrow, treated	pCMVSport 3.0	LP012
HYAA HYAB HYAC	B Cell lymphoma	pCMVSport 3.0	LP012
HWHG HWHH HWHI	Healing groin wound, 6.5 hours post incision	pCMVSport 3.0	LP012
HWHP HWHQ HWHR	Healing groin wound; 7.5 hours post incision	pCMVSport 3.0	LP012
HARM	Healing groin wound - zero hr post-incision (control)	pCMVSport 3.0	LP012
HBIM	Olfactory epithelium; nasalcavity	pCMVSport 3.0	LP012
HWDA	Healing Abdomen wound; 70&90 min post incision	pCMVSport 3.0	LP012
HWEA	Healing Abdomen Wound;15 days post incision	pCMVSport 3.0	LP012
HWJA	Healing Abdomen Wound;21&29 days	pCMVSport 3.0	LP012
HNAL	Human Tongue, frac 2	pSport1	LP012
HMJA	H. Meniingima, M6	pSport1	LP012
HMKA HMKB HMKC HMKD HMKE	H. Meningima, M1	pSport1	LP012
HOFA	Ovarian Tumor I, OV5232	pSport1	LP012
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport1	LP012

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport1	LP012
HMMA HMMB HMMC	Spleen metastic melanoma	pSport1	LP012
HTDA	Human Tonsil, Lib 3	pSport1	LP012
HDBA	Human Fetal Thymus	pSport1	LP012
HDUA	Pericardium	pSport1	LP012
HBZA	Prostate,BPH, Lib 2	pSport1	LP012
HWCA	Larynx tumor	pSport1	LP012
HWKA	Normal lung	pSport1	LP012
HSMB	Bone marrow stroma,treated	pSport1	LP012
HBHM	Normal trachea	pSport1	LP012
HLFC	Human Larynx	pSport1	LP012
HLRB	Siebben Polyposis	pSport1	LP012
HNIA	Mammary Gland	pSport1	LP012
HNJB	Palate carcinoma	pSport1	LP012
HNKA	Palate normal	pSport1	LP012
HMZA	Pharynx carcinoma	pSport1	LP012
HABG	Cheek Carcinoma	pSport1	LP012
HMZM	Pharynx Carcinoma	pSport1	LP012
HDRM	Larynx Carcinoma	pSport1	LP012
HVAA	Pancreas normal PCA4 No	pSport1	LP012
HICA	Tongue carcinoma	pSport1	LP012
HUKA HUKB HUKC HUKD HUKE	Human Uterine Cancer	Lambda ZAP II	LP013
HFFA	Human Fetal Brain, random primed	Lambda ZAP II	LP013
HTUA	Activated T-cell labeled with 4-thioluri	Lambda ZAP II	LP013
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP013
HMEB	Human microvascular Endothelial cells, fract. B	Lambda ZAP II	LP013
HUSH	Human Umbilical Vein Endothelial cells, fract. A, re-excision	Lambda ZAP II	LP013
HLQC HLQD	Hepatocellular tumor, re-excision	Lambda ZAP II	LP013
HTWJ HTWK HTWL	Resting T-cell, re-excision	Lambda ZAP II	LP013
HF6S	Human Whole 6 week Old Embryo (II), subt	pBluescript	LP013
HHPS	Human Hippocampus, subtracted	pBluescript	LP013
HL1S	LNCAP, differential expression	pBluescript	LP013
HLHS HLHT	Early Stage Human Lung, Subtracted	pBluescript	LP013
HSUS	Supt cells, cyclohexamide treated, subtracted	pBluescript	LP013
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBluescript	LP013
HSDS	H. Striatum Depression, subtracted	pBluescript	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HPTZ	Human Pituitary, Subtracted VII	pBluescript	LP013
HSDX	H. Striatum Depression, subt II	pBluescript	LP013
HSDZ	H. Striatum Depression, subt	pBluescript	LP013
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBluescript SK-	LP013
HRTA	Colorectal Tumor	pBluescript SK-	LP013
HSBA HSBB HSBC HSBM	HSC172 cells	pBluescript SK-	LP013
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBluescript SK-	LP013
HJBA HJBB HJBC HJBD	Jurkat T-cell, S1 phase	pBluescript SK-	LP013
HTNA HTNB	Human Thyroid	pBluescript SK-	LP013
HAHA HAHB	Human Adult Heart	Uni-ZAP XR	LP013
HE6A	Whole 6 week Old Embryo	Uni-ZAP XR	LP013
HFCA HFCB HFCC HFCD HFCE	Human Fetal Brain	Uni-ZAP XR	LP013
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP013
HGBA HGBD HGBE HGBF HGBG	Human Gall Bladder	Uni-ZAP XR	LP013
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP013
HTEA HTEB HTEC HTED HTEE	Human Testes	Uni-ZAP XR	LP013
HTTA HTTB HTTC HTTD HTTE	Human Testes Tumor	Uni-ZAP XR	LP013
HYBA HYBB	Human Fetal Bone	Uni-ZAP XR	LP013
HFLA	Human Fetal Liver	Uni-ZAP XR	LP013
HHFB HHFC HHFD HHFE HHFF	Human Fetal Heart	Uni-ZAP XR	LP013
HUVB HUVC HUVD HUVE	Human Umbilical Vein, End. remake	Uni-ZAP XR	LP013
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP013
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP013
HTAA HTAB HTAC HTAD HTAE	Human Activated T-cells	Uni-ZAP XR	LP013
HFEA HFEB HFEC	Human Fetal Epithelium (skin)	Uni-ZAP XR	LP013
HJPA HJPB HJPC HJPD	Human Jurkat Membrane Bound Polysomes	Uni-ZAP XR	LP013
HESA	Human Epithelioid Sarcoma	Uni-ZAP XR	LP013
HALS	Human Adult Liver, Subtracted	Uni-ZAP XR	LP013
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP013
HCAA HCAB HCAC	Cem cells, cyclohexamide treated	Uni-ZAP XR	LP013
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP013
HE9A HE9B HE9C HE9D HE9E	Nine Week Old Early Stage Human	Uni-ZAP XR	LP013
HSFA	Human Fibrosarcoma	Uni-ZAP XR	LP013
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP013
HTRA	Human Trachea Tumor	Uni-ZAP XR	LP013
HE2A HE2D HE2E HE2H HE2I	12 Week Old Early Stage	Uni-ZAP XR	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	Human		
HE2B HE2C HE2F HE2G HE2P	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP013
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP013
HBGA	Human Primary Breast Cancer	Uni-ZAP XR	LP013
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP013
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP013
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP013
HTOA HTOD HTOE HTOF HTOG	human tonsils	Uni-ZAP XR	LP013
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP013
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP013
HOQB	Human OB HOS treated (1 nM E2) fraction I	Uni-ZAP XR	LP013
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP013
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP013
HROA HROC	HUMAN STOMACH	Uni-ZAP XR	LP013
HBJA HBJB HBJC HBJD HBJE	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP013
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP013
HCPA	Corpus Callosum	Uni-ZAP XR	LP013
HSOA	stomach cancer (human)	Uni-ZAP XR	LP013
HERA	SKIN	Uni-ZAP XR	LP013
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP013
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP013
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP013
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP013
HAPN HAPO HAPP HAPQ HAPR	Human Adult Pulmonary;re-excision	Uni-ZAP XR	LP013
HLTG HLTH	Human T-cell lymphoma;re-excision	Uni-ZAP XR	LP013
HAHC HAHD HAHE	Human Adult Heart;re-excision	Uni-ZAP XR	LP013
HAGA HAGB HAGC HAGD HAGE	Human Amygdala	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP013
HSHA HSHB HSHC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP013
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP013
HPIA HPIB HPIC	LNCAP prostate cell line	Uni-ZAP XR	LP013
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP013
HBTA	Bone Marrow Stroma, TNF&LPS ind	Uni-ZAP XR	LP013
HMCF HMCG HMCH HMCI HMCJ	Macrophage-oxLDL; re-excision	Uni-ZAP XR	LP013
HAGG HAGH HAGI	Human Amygdala;re-excision	Uni-ZAP XR	LP013
HACA	H. Adipose Tissue	Uni-ZAP XR	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HKFB	K562 + PMA (36 hrs),re-excision	ZAP Express	LP013
HCWT HCWU HCWV	CD34 positive cells (cord blood),re-ex	ZAP Express	LP013
HBWA	Whole brain	ZAP Express	LP013
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP013
HAVM	Temporal cortex-Alzheizmer	pT-Adv	LP014
HAVT	Hippocampus, Alzheimer Subtracted	pT-Adv	LP014
HHAS	CHME Cell Line	Uni-ZAP XR	LP014
HAJR	Larynx normal	pSport 1	LP014
HWLE HWLF HWLG HWLH	Colon Normal	pSport 1	LP014
HCRM HCRN HCRO	Colon Carcinoma	pSport 1	LP014
HWLI HWLJ HWLK	Colon Normal	pSport 1	LP014
HWLQ HWLR HWLS HWLT	Colon Tumor	pSport 1	LP014
HBFM	Gastrocnemius Muscle	pSport 1	LP014
HBOD HBOE	Quadriceps Muscle	pSport 1	LP014
HBKD HBKE	Soleus Muscle	pSport 1	LP014
HCCM	Pancreatic Langerhans	pSport 1	LP014
HWGA	Larynx carcinoma	pSport 1	LP014
HWGM HWGN	Larynx carcinoma	pSport 1	LP014
HWLA HWLB HWLC	Normal colon	pSport 1	LP014
HWLM HWLN	Colon Tumor	pSport 1	LP014
HVAM HVAN HVAO	Pancreas Tumor	pSport 1	LP014
HWGQ	Larynx carcinoma	pSport 1	LP014
HAQM HAQN	Salivary Gland	pSport 1	LP014
HASM	Stomach; normal	pSport 1	LP014
HBCM	Uterus; normal	pSport 1	LP014
HCDM	Testis; normal	pSport 1	LP014
HDJM	Brain; normal	pSport 1	LP014
HEFM	Adrenal Gland,normal	pSport 1	LP014
HBAA	Rectum normal	pSport 1	LP014
HFDM	Rectum tumour	pSport 1	LP014
HGAM	Colon, normal	pSport 1	LP014
HHMM	Colon, tumour	pSport 1	LP014
HCLB HCLC	Human Lung Cancer	Lambda Zap II	LP015
HRLA	L1 Cell line	ZAP Express	LP015
HHAM	Hypothalamus, Alzheimer's	pCMVSport 3.0	LP015
HKBA	Ku 812F Basophils Line	pSport 1	LP015
HS2S	Saos2, Dexamethosome Treated	pSport 1	LP016
HA5A	Lung Carcinoma A549 TNFalpha activated	pSport 1	LP016
HTFM	TF-1 Cell Line GM-CSF Treated	pSport 1	LP016
HYAS	Thyroid Tumour	pSport 1	LP016
HUTS	Larynx Normal	pSport 1	LP016
HXOA	Larynx Tumor	pSport 1	LP016
HEAH	Ea.hy.926 cell line	pSport 1	LP016
HINA	Adenocarcinoma Human	pSport 1	LP016
HRMA	Lung Mesothelium	pSport 1	LP016

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HLCL	Human Pre-Differentiated Adipocytes	Uni-Zap XR	LP017
HS2A	Saos2 Cells	pSport 1	LP020
HS2I	Saos2 Cells; Vitamin D3 Treated	pSport 1	LP020
HUCM	CHME Cell Line, untreated	pSport 1	LP020
HEPN	Aryepiglottis Normal	pSport 1	LP020
HPSN	Sinus Piniformis Tumour	pSport 1	LP020
HNSA	Stomach Normal	pSport 1	LP020
HNSM	Stomach Tumour	pSport 1	LP020
HNLA	Liver Normal Met5No	pSport 1	LP020
HUTA	Liver Tumour Met 5 Tu	pSport 1	LP020
HOCN	Colon Normal	pSport 1	LP020
HOCT	Colon Tumor	pSport 1	LP020
HTNT	Tongue Tumour	pSport 1	LP020
HLXN	Larynx Normal	pSport 1	LP020
HLXT	Larynx Tumour	pSport 1	LP020
HTYN	Thymus	pSport 1	LP020
HPLN	Placenta	pSport 1	LP020
HTNG	Tongue Normal	pSport 1	LP020
HZAA	Thyroid Normal (SDCA2 No)	pSport 1	LP020
HWES	Thyroid Thyroiditis	pSport 1	LP020
HFHD	Ficolled Human Stromal Cells, 5Fu treated	pTrip1Ex2	LP021
HFHM,HFHN	Ficolled Human Stromal Cells, Untreated	pTrip1Ex2	LP021
HPCI	Hep G2 Cells, lambda library	lambda Zap-CMV XR	LP021
HBCA,HBCB,HBCC	H. Lymph node breast Cancer	Uni-ZAP XR	LP021
HCOK	Chondrocytes	pSPORT1	LP022
HDCA, HDCB, HDCC	Dendritic Cells From CD34 Cells	pSPORT1	LP022
HDMA, HDMB	CD40 activated monocyte dendritic cells	pSPORT1	LP022
HDDM, HDDN, HDDO	LPS activated derived dendritic cells	pSPORT1	LP022
HPCR	Hep G2 Cells, PCR library	lambda Zap-CMV XR	LP022
HAAA, HAAB, HAAC	Lung, Cancer (4005313A3): Invasive Poorly Differentiated Lung Adenocarcinoma	pSPORT1	LP022
HIPA, HIPB, HIPC	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic	pSPORT1	LP022
HOOH, HOOI	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot	pSPORT1	LP022
HIDA	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HUJA,HUJB,HUJC,HUJD,HUJE	B-Cells	pCMVSport 3.0	LP022
HNOA,HNOB,HNOC,HNOD	Ovary, Normal: (9805C040R)	pSPORT1	LP022

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HNLM	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HSCL	Stromal Cells	pSPORT1	LP022
HAAX	Lung, Cancer: (4005313 A3) Invasive Poorly-differentiated Metastatic lung adenocarcinoma	pSPORT1	LP022
HUUA,HUUB,HUUC,HUUD	B-cells (unstimulated)	pTrip1Ex2	LP022
HWWA,HWWB,HWWC,HWWD,HWWE,HWWF,HWWG	B-cells (stimulated)	pSPORT1	LP022
HCCC	Colon, Cancer: (9808C064R)	pCMVSport 3.0	LP023
HPDO HPDP HPDQ HPDR HPD	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	pSport 1	LP023
HPCO HPCP HPCQ HPCT	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	pSport 1	LP023
HOCM HOCO HOCP HOCQ	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	pSport 1	LP023
HCBM HCBN HCBO	Breast, Cancer: (4004943 A5)	pSport 1	LP023
HNBT HNBU HNBV	Breast, Normal: (4005522B2)	pSport 1	LP023
HBCP HBCQ	Breast, Cancer: (4005522 A2)	pSport 1	LP023
HBCJ	Breast, Cancer: (9806C012R)	pSport 1	LP023
HSAM HSAN	Stromal cells 3.88	pSport 1	LP023
HVCA HVCB HVCC HVCD	Ovary, Cancer: (4004332 A2)	pSport 1	LP023
HSCK HSEN HSEO	Stromal cells (HBM3.18)	pSport 1	LP023
HSCP HSCQ	stromal cell clone 2.5	pSport 1	LP023
HUXA	Breast Cancer: (4005385 A2)	pSport 1	LP023
HCOM HCON HCOO HCOP HCOQ	Ovary, Cancer (4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	pSport 1	LP023
HBNM	Breast, Cancer: (9802C020E)	pSport 1	LP023
HVVA HVVB HVVC HVVD HVVE	Human Bone Marrow, treated	pSport 1	LP023

Two nonlimiting examples are provided below for isolating a particular clone from the deposited sample of plasmid cDNAs cited for that clone in Table 7. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to the nucleotide sequence of SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982)). The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection

agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the nucleotide sequence of SEQ ID NO:X are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993)).

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide

and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the sequence corresponding to SEQ ID NO:X according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue specific expression analysis

The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue and/or disease specific cDNA libraries. Libraries generated from a particular tissue are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs and assembled contigs which show tissue specific expression are selected.

The original clone from which the specific EST sequence was generated, or in the case of an assembled contig, the clone from which the 5' most EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured and then transferred in 96 or 384 well format to a nylon membrane (Schleicher and Scheull) generating an array filter of tissue specific clones. Housekeeping genes, maize genes, and known tissue specific genes are included on the filters. These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed (e.g., prostate, prostate cancer, ovarian, ovarian cancer, etc.). The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions: 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions are analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 ($O.D.^{600}$) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8. The column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector, called pHE4a (ATCC Accession Number 209645, deposited on February 25, 1998) which contains phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter and operator sequences are made synthetically.

DNA can be inserted into the pHE4a by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0.

Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 μg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five μg of a plasmid containing the polynucleotide is co-transfected with 1.0 μg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA, Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μg of BaculoGold™ virus DNA and 5 μg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μl Lipofectin plus 90 μl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 μl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 μCi of ^{35}S-methionine and 5 μCi ^{35}S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et

al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991)). Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 μg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates

(Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μM, 2 μM, 5 μM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988)). Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time *in vivo*. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (ATCC Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the polypeptide of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO: 1)

Example 10: Production of an Antibody from a Polypeptide

a) Hybridoma Technology

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing a polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of a polypeptide of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for a polypeptide of the present invention are prepared using hybridoma technology (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with a polypeptide of the present invention or, more preferably, with a secreted polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 μg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention .

Alternatively, additional antibodies capable of binding to a polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide-specific antibody can be blocked by said polypeptide. Such antibodies comprise anti-idiotypic antibodies to the polypeptide-specific antibody and are used to immunize an animal to induce formation of further polypeptide-specific antibodies.

For *in vivo* use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al.; International Publication No. WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985)).

b) Isolation Of Antibody Fragments Directed Against a Polypeptide of the Present Invention From A Library Of scFvs

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against a polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in International Publication No. WO 92/01047. To rescue phage displaying antibody fragments, approximately 10^9 *E. coli* harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 μg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 108

TU of delta gene 3 helper (M13 delta gene III, see International Publication No. WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 μg/ml ampicillin and 50 ug/ml kanamycin and grown overnight. Phage are prepared as described in International Publication No. WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10^{13} transducing units/ml (ampicillin-resistant clones).

Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10^{13} TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., International Publication No. WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding

affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a gastrointestinal disease or disorder is isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X; and/or the nucleotide sequence of the cDNA contained in ATCC Deposit No:Z. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase (Epicentre Technologies). The intron-exon boundaries of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations are then cloned and sequenced to validate the results of the direct sequencing.

PCR products are cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Manheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991)). Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbound conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 13: Formulation

The invention also provides methods of preventing, treating and/or ameliorating a gastrointestinal disease or disorder by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration,

the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Therapeutics can be are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res.

15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

In a preferred embodiment, polypeptide, polynucleotide, and antibody compositions of the invention are formulated in a biodegradable, polymeric drug delivery system, for example as described in U.S. Patent Nos. 4,938,763; 5,278,201; 5,278,202; 5,324,519; 5,340,849; and 5,487,897 and in International Publication Numbers WO01/35929, WO00/24374, and WO00/06117 which are hereby incorporated by reference in their entirety. In specific preferred embodiments the polypeptide, polynucleotide, and antibody compositions of the invention are formulated using the ATRIGEL® Biodegradable System of Atrix Laboratories, Inc. (Fort Collins, Colorado).

Examples of biodegradable polymers which can be used in the formulation of polypeptide, polynucleotide, and antibody compositions, include but are not limited to, polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures of the above materials. The preferred polymers are those that have a lower degree of crystallization and are more hydrophobic. These polymers and copolymers are more soluble in the biocompatible solvents than the highly crystalline polymers such as polyglycolide and chitin which also have a high degree of hydrogen-bonding. Preferred materials with the desired solubility parameters are the polylactides, polycaprolactones, and copolymers of these with glycolide in which there are more amorphous regions to enhance solubility. In specific preferred embodiments, the biodegradable polymers which can be used in the formulation of polypeptide, polynucleotide, and antibody compositions are poly(lactide-co-glycolides). Polymer properties such as molecular weight, hydrophobicity, and lactide/glycolide ratio may be modified to obtain the desired polypeptide, polynucleotide, or antibody release profile (See, e.g., Ravivarapu et al., Journal of Pharmaceutical Sciences 89:732-741 (2000), which is hereby incorporated by reference in its entirety).

It is also preferred that the solvent for the biodegradable polymer be non-toxic, water miscible, and otherwise biocompatible. Examples of such solvents include, but are not limited to, N-methyl-2-pyrrolidone, 2-pyrrolidone, C2 to C6 alkanols, C1 to C15 alchohols, dils, triols, and tetraols such as ethanol, glycerine propylene glycol, butanol; C3 to C15 alkyl ketones such as acetone, diethyl ketone and methyl ethyl ketone; C3 to C15 esters such as methyl acetate, ethyl acetate, ethyl lactate; alkyl ketones such as methyl ethyl ketone, C1 to C15 amides such as dimethylformamide, dimethylacetamide and caprolactam; C3 to C20 ethers such as tetrahydrofuran, or solketal; tweens, triacetin, propylene carbonate, decylmethylsulfoxide,

dimethyl sulfoxide, oleic acid, 1-dodecylazacycloheptan-2-one, Other preferred solvents are benzyl alchohol, benzyl benzoate, dipropylene glycol, tributyrin, ethyl oleate, glycerin, glycofural, isopropyl myristate, isopropyl palmitate, oleic acid, polyethylene glycol, propylene carbonate, and triethyl citrate. The most preferred solvents are N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, triacetin, and propylene carbonate because of the solvating ability and their compatibility.

Additionally, formulations comprising polypeptide, polynucleotide, and antibody compositions and a biodegradable polymer may also include release-rate modification agents and/or pore-forming agents. Examples of release-rate modification agents include, but are not limited to, fatty acids, triglycerides, other like hydrophobic compounds, organic solvents, plasticizing compounds and hydrophilic compounds. Suitable release rate modification agents include, for example, esters of mono-, di-, and tricarboxylic acids, such as 2-ethoxyethyl acetate, methyl acetate, ethyl acetate, diethyl phthalate, dimethyl phthalate, dibutyl phthalate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, glycerol triacetate, di(n-butyl) sebecate, and the like; polyhydroxy alcohols, such as propylene glycol, polyethylene glycol, glycerin, sorbitol, and the like; fatty acids; triesters of glycerol, such as triglycerides, epoxidized soybean oil, and other epoxidized vegetable oils; sterols, such as cholesterol; alcohols, such as C.sub.6 -C.sub.12 alkanols, 2-ethoxyethanol. The release rate modification agent may be used singly or in combination with other such agents. Suitable combinations of release rate modification agents include, but are not limited to, glycerin/propylene glycol, sorbitol/glycerine, ethylene oxide/propylene oxide, butylene glycol/adipic acid, and the like. Preferred release rate modification agents include, but are not limited to, dimethyl citrate, triethyl citrate, ethyl heptanoate, glycerin, and hexanediol. Suitable pore-forming agents that may be used in the polymer composition include, but are not limited to, sugars such as sucrose and dextrose, salts such as sodium chloride and sodium carbonate, polymers such as hydroxylpropylcellulose, carboxymethylcellulose, polyethylene glycol, and polyvinylpyrrolidone. Solid crystals that will provide a defined pore size, such as salt or sugar, are preferred.

In specific preferred embodiments the polypeptide, polynucleotide, and antibody compositions of the invention are formulated using the BEMA™ BioErodible Mucoadhesive System, MCA™ MucoCutaneous Absorption System, SMP™ Solvent MicroParticle System, or BCP™ BioCompatible Polymer System of Atrix Laboratories, Inc. (Fort Collins, Colorado).

Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985);

Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable prepartions of *Corynebacterium parvum*. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the

Therapeutics of the invention, include but not limited to, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the Therapeutics of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the compositions of the invention include, but are not limited to, heparin, low molecular weight heparin, warfarin sodium (e.g., COUMADIN®), dicumarol, 4-hydroxycoumarin, anisindione (e.g., MIRADON™), acenocoumarol (e.g., nicoumalone, SINTHROME™), indan-1,3-dione, phenprocoumon (e.g., MARCUMAR™), ethyl biscoumacetate (e.g., TROMEXAN™), and aspirin. In a specific embodiment, compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, compositions of the invention are administered in combination with heparin. In another specific embodiment, compositions of the invention are administered in combination with heparin and aspirin.

In another embodiment, the Therapeutics of the invention are administered in combination with thrombolytic drugs. Thrombolytic drugs that may be administered with the compositions of the invention include, but are not limited to, plasminogen, lys-plasminogen, alpha2-antiplasmin, streptokinae (e.g., KABIKINASE™), antiresplace (e.g., EMINASE™), tissue plasminogen activator (t-PA, altevase, ACTIVASE™), urokinase (e.g., ABBOKINASE™), sauruplase, (Prourokinase, single chain urokinase), and aminocaproic acid (e.g., AMICAR™). In a specific embodiment, compositions of the invention are administered in combination with tissue plasminogen activator and aspirin.

In another embodiment, the Therapeutics of the invention are administered in combination with antiplatelet drugs. Antiplatelet drugs that may be administered with the compositions of the invention include, but are not limited to, aspirin, dipyridamole (e.g., PERSANTINE™), and ticlopidine (e.g., TICLID™).

In specific embodiments, the use of anti-coagulants, thrombolytic and/or antiplatelet drugs in combination with Therapeutics of the invention is contemplated for the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of thrombosis, arterial thrombosis,

venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the use of anticoagulants, thrombolytic drugs and/or antiplatelet drugs in combination with Therapeutics of the invention is contemplated for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the therapeutics of the invention, alone or in combination with antiplatelet, anticoagulant, and/or thrombolytic drugs, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott; COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead); DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome

Inc.); CS-87 (3'azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of β-L-FD4C and β-L-FddC (WO 98/17281).

Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and Propolis (WO 99/49830).

Additional protease inhibitors include LOPINAVIR™ (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myres Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity against protease inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Welcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine recpetor agonists such as RANTES, SDF-1, MIP-1α, MIP-1β, etc., may also inhibit fusion.

Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones; ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at

cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

Additional antiretroviral agents include hydroxyurea-like compunds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors sucha as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1α, MIP-1β, SDF-1α, IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN-α2a; antagonists of TNFs, NFκB, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targetted to the ER to block surface expression of newly synthesized CCR5 (Yang *et al., PNAS 94*:11567-72 (1997); Chen *et al., Nat. Med. 3*:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF-α antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and α-naphthoflavone (WO 98/30213); and antioxidants such as γ-L-glutamyl-L-cysteine ethyl ester (γ-GCE; WO 99/56764).

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol,

cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

In other embodiments, the Therapeutics of the invention are administered in combination with immunestimulants. Immunostimulants that may be administered in combination with the Therapeutics of the invention include, but are not limited to, levamisole (e.g., ERGAMISOL™), isoprinosine (e.g. INOSIPLEX™), interferons (e.g. interferon alpha), and interleukins (e.g., IL-2).

In other embodiments, Therapeutics of the invention are administered in combination with immunosuppressive agents. Immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate motefil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™ (antithymocyte glubulin), and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

In certain embodiments, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin,

ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolmidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

Anti-angiogenic agents that may be administed in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositons of the invention include, but are not lmited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat

(British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositons of the invention include, but are not lmited to, EMD-121974 (Merck KcgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositons of the invention include, but are not lmited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositons of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcolysin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin

(streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouacil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone proprionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing horomone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are

administered in combination with tositumomab. In a further embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more radisotopes. Particularly preferred isotopes are ^{90}Y and ^{111}In.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-

B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

In certain embodiments, Therapeutics of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

In another embodiment, the Therapeutics of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amidoarone, bretylium, digitalis, digoxin, digitoxin, diliazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

In another embodiment, the Therapeutics of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorphenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit Na^+-K^+-$2Cl^-$ symport (e.g., furosemide, bumetanide, azosemide, piretanide, tripamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, ^{127}I, radioactive isotopes of iodine such as ^{131}I and ^{123}I; recombinant growth hormone, such as HUMATROPE™ (recombinant somatropin); growth hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T_4™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T_3™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-*n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca^{2+} channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or congugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and

VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone), LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotropic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)),

HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone); bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), ciglitazone, pioglitazone, and alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide).

In an additional embodiment, the Therapeutics of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL™), ferrous fumarate (e.g., FEOSTAT™), ferrous gluconate (e.g., FERGON™), polysaccharide-iron complex (e.g., NIFEREX™), iron dextran injection (e.g., INFED™), cupric sulfate, pyroxidine, riboflavin, Vitamin B_{12}, cyancobalamin injection (e.g., REDISOL™, RUBRAMIN PC™), hydroxocobalamin, folic acid

(e.g., FOLVITE™), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

In another embodiment, Therapeutics of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents. Vasodilating agents that may be administered with the Therapeutics of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

In certain embodiments, the Therapeutics of the invention are administered in combination with treatments for gastrointestinal disorders. Treatments for gastrointestinal disorders that may be administered with the Therapeutic of the invention include, but are not limited to, H_2 histamine receptor antagonists (e.g., TAGAMET™ (cimetidine), ZANTAC™ (ranitidine), PEPCID™ (famotidine), and AXID™ (nizatidine)); inhibitors of H^+, K^+ ATPase (e.g., PREVACID™ (lansoprazole) and PRILOSEC™ (omeprazole)); Bismuth compounds (e.g., PEPTO-BISMOL™ (bismuth subsalicylate) and DE-NOL™ (bismuth subcitrate)); various antacids; sucralfate; prostaglandin analogs (e.g. CYTOTEC™ (misoprostol)); muscarinic cholinergic antagonists; laxatives (e.g., surfactant laxatives, stimulant laxatives, saline and osmotic laxatives); antidiarrheal agents (e.g., LOMOTIL™ (diphenoxylate), MOTOFEN™ (diphenoxin), and IMODIUM™ (loperamide hydrochloride)), synthetic analogs of somatostatin such as SANDOSTATIN™ (octreotide), antiemetic agents (e.g., ZOFRAN™ (ondansetron), KYTRIL™ (granisetron hydrochloride), tropisetron, dolasetron, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, triflupromazine, domperidone, haloperidol, droperidol, trimethobenzamide, dexamethasone, methylprednisolone, dronabinol, and nabilone); D2 antagonists (e.g., metoclopramide, trimethobenzamide and chlorpromazine); bile salts; chenodeoxycholic acid; ursodeoxycholic acid; and pancreatic enzyme preparations such as pancreatin and pancrelipase.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Example 14: Method of Treating Decreased Levels of the Polypeptide

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of polypeptides (including agonists thereto), and/or antibodies of the invention. Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide of the present invention in an individual may be treated by administering agonists of said polypeptide. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist (including polypeptides and antibodies of the present invention) to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

Example 15: Method of Treating Increased Levels of the Polypeptide

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The antisense polynucleotides of the present invention can be formulated using techniques and formulations described herein (e.g. see Example 13), or otherwise known in the art.

Example 16: Method of Treatment Using Gene Therapy-Ex Vivo

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are

placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention

Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel, then purified by phenol extraction and ethanol precipitation.

In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are

trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na_2 HPO_4, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately $3X10^6$ cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3'end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 μg/ml. 0.5 ml of the cell suspension (containing approximately $1.5X10^6$ cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μF and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 18: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to prevent, treat, and/or ameliorate gastrointestinal diseases and disorders. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to (i.e., associated with) a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within an animal, including muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic

channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages

and other treatment parameters in humans and other animals using naked DNA.

Example 19: Transgenic Animals

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene,

gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 20: Knock-Out Animals

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (e.g., see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell

5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host

immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 21: Production Of Polypeptide of the Invention For High-Throughput Screening Assays

The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 32-41.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2 x 10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First,

person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl2 (anhyd); 0.00130 mg/L $CuSO_4$-$5H_2O$; 0.050 mg/L of $Fe(NO_3)_3$-$9H_2O$; 0.417 mg/L of $FeSO_4$-$7H_2O$; 311.80 mg/L of Kcl; 28.64 mg/L of $MgCl_2$; 48.84 mg/L of $MgSO_4$; 6995.50 mg/L of NaCl; 2400.0 mg/L of $NaHCO_3$; 62.50 mg/L of NaH_2PO_4-H_20; 71.02 mg/L of Na_2HPO4; .4320 mg/L of $ZnSO_4$-$7H_2O$; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H_20; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H_20; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H_20; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalainine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tryrosine-2Na-$2H_20$; and 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B_{12}; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml

appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 32-39.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 22: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995)). A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and

one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xaa-Trp-Ser (SEQ ID NO: 2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway (See Table below). Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

Ligand	tyk2	JAKs Jak1	Jak2	Jak3	STATS	GAS(elements) or ISRE
IFN family						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
Il-10	+	?	?	-	1,3	
gp130 family						
IL-6 (Pleiotropic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
Il-11(Pleiotropic)	?	+	?	?	1,3	
OnM(Pleiotropic)	?	+	+	?	1,3	
LIF(Pleiotropic)	?	+	+	?	1,3	
CNTF(Pleiotropic)	-/+	+	+	?	1,3	
G-CSF(Pleiotropic)	?	+	?	?	1,3	
IL-12(Pleiotropic)	+	-	+	+	1,3	
g-C family						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
gp140 family						
IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
Growth hormone family						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
Receptor Tyrosine Kinases						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 32-33, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO: 3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO: 4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':<u>CTCGAG</u>ATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAA<u>AAGCTT</u>:3' (SEQ ID NO: 5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this

vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 32-33.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing EGR and NF-KB promoter sequences are described in Examples 34 and 35. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 23: Assay for SEAP Activity

As a reporter molecule for the assays described in Examples 32-35, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the Table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on a luminometer, thus one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5

17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 24: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any

fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO_2 incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO_2 incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular Ca^{++} concentration.

Example 25: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 21, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN)) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4^{o}C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well,

after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg_{2+} (5mM ATP/50mM $MgCl_2$), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM $MgCl_2$, 5 mM $MnCl_2$, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 26: High-Throughput Screening Assay Identifying Phosphorylation Activity

As a potential alternative and/or complement to the assay of protein tyrosine kinase activity described in Example 25, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below

one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 21 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

Example 27: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may

adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 μl of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μl volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 μl of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 μl of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 μl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 μl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μl of pNNP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 μl of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

Example 28: Alamar Blue Endothelial Cells Proliferation Assay

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard

Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37 degreesC overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form (i.e., stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity). The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

Example 29: Detection of Inhibition of a Mixed Lymphocyte Reaction

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases

associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM®, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2 x 10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2 x 10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μl) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μg/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 μg/ml. Cells are cultured for 7-8 days at 37°C in 5% CO_2, and 1 μC of [^{3}H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 30: Assays for Protease Activity

The following assay may be used to assess protease activity of the polypeptides of the invention.

Gelatin and casein zymography are performed essentially as described (Heusen et al., *Anal. Biochem.*, 102:196-202 (1980); Wilson et al., *Journal of Urology*, 149:653-658 (1993)). Samples are run on 10% polyacryamide/0.1% SDS gels containing 1% gelain orcasein, soaked in 2.5% triton at room temperature for 1 hour, and in 0.1M glycine, pH 8.3 at 37°C 5 to 16 hours.

After staining in amido black areas of proteolysis apear as clear areas agains the blue-black background. Trypsin (Sigma T8642) is used as a positive control.

Protease activity is also determined by monitoring the cleavage of n-a-benzoyl-L-arginine ethyl ester (BAEE) (Sigma B-4500. Reactions are set up in (25mMNaPO$_4$,1mM EDTA, and 1mM BAEE), pH 7.5. Samples are added and the change in adsorbance at 260nm is monitored on the Beckman DU-6 spectrophotometer in the time-drive mode. Trypsin is used as a positive control.

Additional assays based upon the release of acid-soluble peptides from casein or hemoglobin measured as adsorbance at 280 nm or colorimetrically using the Folin method are performed as described in Bergmeyer, et al., *Methods of Enzymatic Analysis*, 5 (1984). Other assays involve the solubilization of chromogenic substrates (Ward, *Applied Science*, 251-317 (1983)).

Example 31: Identifying Serine Protease Substrate Specificity

Methods known in the art or described herein may be used to determine the substrate specificity of the polypeptides of the present invention having serine protease activity. A preferred method of determining substrate specificity is by the use of positional scanning synthetic combinatorial libraries as described in GB 2 324 529 (incorporated herein in its entirety).

Example 32: Ligand Binding Assays

The following assay may be used to assess ligand binding activity of the polypeptides of the invention.

Ligand binding assays provide a direct method for ascertaining receptor pharmacology and are adaptable to a high throughput format. The purified ligand for a polypeptide is radiolabeled to high specific activity (50-2000 Ci/mmol) for binding studies. A determination is then made that the process of radiolabeling does not diminish the activity of the ligand towards its polypeptide. Assay conditions for buffers, ions, pH and other modulators such as nucleotides are optimized to establish a workable signal to noise ratio for both membrane and whole cell polypeptide sources. For these assays, specific polypeptide binding is defined as total associated radioactivity minus the radioactivity measured in the presence of an excess of unlabeled competing ligand. Where possible, more than one competing ligand is used to define residual nonspecific binding.

Example 33: Functional Assay in Xenopus Oocytes

Capped RNA transcripts from linearized plasmid templates encoding the polypeptides of the invention are synthesized in vitro with RNA polymerases in accordance with standard procedures. In vitro transcripts are suspended in water at a final concentration of 0.2 mg/mi. Ovarian lobes are removed from adult female toads, Stage V defolliculated oocytes are obtained, and RNA transcripts (10 ng/oocytc) are injected in a 50 nl bolus using a microinjection apparatus. Two electrode voltage clamps are used to measure the currents from individual *Xenopus oocytes* in response polypeptides and polypeptide agonist exposure. Recordings are made in Ca2+ free Barth's medium at room temperature. The Xenopus system can be used to screen known ligands and tissue/cell extracts for activating ligands.

Example 34: Microphysiometric Assays

Activation of a wide variety of secondary messenger systems results in extrusion of small amounts of acid from a cell. The acid formed is largely as a result of the increased metabolic activity required to fuel the intracellular signaling process. The pH changes in the media surrounding the cell are very small but are detectable by the CYTOSENSOR microphysiometer (Molecular Devices Ltd., Menlo Park, Calif.). The CYTOSENSOR is thus capable of detecting the activation of polypeptide which is coupled to an energy utilizing intracellular signaling pathway.

Example 35: Extract/Cell Supernatant Screening

A large number of mammalian receptors exist for which there remains, as yet, no cognate activating ligand (agonist). Thus, active ligands for these receptors may not be included within the ligands banks as identified to date. Accordingly, the polypeptides of the invention can also be functionally screened (using calcium, cAMP, microphysiometer, oocyte electrophysiology, etc., functional screens) against tissue extracts to identify its natural ligands. Extracts that produce positive functional responses can be sequentially subfractionated until an activating ligand is isolated and identified.

Example 36: Calcium and cAMP Functional Assays

Seven transmembrane receptors which are expressed in HEK 293 cells have been shown to be coupled functionally to activation of PLC and calcium mobilization and/or cAMP stimulation or inhibition. Basal calcium levels in the HEK 293 cells in receptor-transfected or vector control

cells were observed to be in the normal, 100 nM to 200 nM, range. HEK 293 cells expressing recombinant receptors are loaded with fura 2 and in a single day >150 selected ligands or tissue/cell extracts are evaluated for agonist induced calcium mobilization. Similarly, HEK 293 cells expressing recombinant receptors are evaluated for the stimulation or inhibition of cAMP production using standard cAMP quantitation assays. Agonists presenting a calcium transient or cAMP fluctuation are tested in vector control cells to determine if the response is unique to the transfected cells expressing receptor.

Example 37: ATP-binding assay

The following assay may be used to assess ATP-binding activity of polypeptides of the invention.

ATP-binding activity of the polypeptides of the invention may be detected using the ATP-binding assay described in U.S. Patent 5,858,719, which is herein incorporated by reference in its entirety. Briefly, ATP-binding to polypeptides of the invention is measured via photoaffinity labeling with 8-azido-ATP in a competition assay. Reaction mixtures containing 1 mg/ml of the ABC transport protein of the present invention are incubated with varying concentrations of ATP, or the non-hydrolyzable ATP analog adenyl-5'-imidodiphosphate for 10 minutes at 4°C. A mixture of 8-azido-ATP (Sigma Chem. Corp., St. Louis, MO.) plus 8-azido-ATP (^{32}P-ATP) (5 mCi/μmol, ICN, Irvine CA.) is added to a final concentration of 100 μM and 0.5 ml aliquots are placed in the wells of a porcelain spot plate on ice. The plate is irradiated using a short wave 254 nm UV lamp at a distance of 2.5 cm from the plate for two one-minute intervals with a one-minute cooling interval in between. The reaction is stopped by addition of dithiothreitol to a final concentration of 2mM. The incubations are subjected to SDS-PAGE electrophoresis, dried, and autoradiographed. Protein bands corresponding to the particular polypeptides of the invention are excised, and the radioactivity quantified. A decrease in radioactivity with increasing ATP or adenly-5'-imidodiphosphate provides a measure of ATP affinity to the polypeptides.

Example 38: Small Molecule Screening

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug

screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and polypeptide of the invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the invention. These methods comprise contacting such an agent with a polypeptide of the invention or fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is herein incorporated by reference in its entirety. Briefly stated, large numbers of different small molecule test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The test compounds are reacted with polypeptides of the invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Example 39: Phosphorylation Assay

In order to assay for phosphorylation activity of the polypeptides of the invention, a phosphorylation assay as described in U.S. Patent 5,958,405 (which is herein incorporated by reference) is utilized. Briefly, phosphorylation activity may be measured by phosphorylation of a protein substrate using gamma-labeled ^{32}P-ATP and quantitation of the incorporated radioactivity using a gamma radioisotope counter. The polypeptides of the invention are incubated with the protein substrate, ^{32}P-ATP, and a kinase buffer. The ^{32}P incorporated into the substrate is then

separated from free ^{32}P-ATP by electrophoresis, and the incorporated ^{32}P is counted and compared to a negative control. Radioactivity counts above the negative control are indicative of phosphorylation activity of the polypeptides of the invention.

Example 40: Detection of Phosphorylation Activity (Activation) of the Polypeptides of the Invention in the Presence of Polypeptide Ligands

Methods known in the art or described herein may be used to determine the phosphorylation activity of the polypeptides of the invention. A preferred method of determining phosphorylation activity is by the use of the tyrosine phosphorylation assay as described in US 5,817,471 (incorporated herein by reference).

Example 41: Identification Of Signal Transduction Proteins That Interact With Polypeptides Of The Present Invention

The purified polypeptides of the invention are research tools for the identification, characterization and purification of additional signal transduction pathway proteins or receptor proteins. Briefly, labeled polypeptides of the invention are useful as reagents for the purification of molecules with which it interacts. In one embodiment of affinity purification, polypeptides of the invention are covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as carcinoma tissues, is passed over the column, and molecules with appropriate affinity bind to the polypeptides of the invention. The protein complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

Example 42: Assay for Phosphatase Activity

The following assay may be used to assess serine/threonine phosphatase (PTPase) activity of the polypeptides of the invention.

In order to assay for serine/threonine phosphatase (PTPase) activity, assays can be utilized which are widely known to those skilled in the art. For example, the serine/threonine phosphatase (PSPase) activity is measured using a PSPase assay kit from New England Biolabs, Inc. Myelin basic protein (MyBP), a substrate for PSPase, is phosphorylated on serine and threonine residues

with cAMP-dependent Protein Kinase in the presence of [^{32}P]ATP. Protein serine/threonine phosphatase activity is then determined by measuring the release of inorganic phosphate from 32P-labeled MyBP.

Example 43: Interaction of Serine/Threonine Phosphatases with other Proteins

The polypeptides of the invention with serine/threonine phosphatase activity as determined in Example 42 are research tools for the identification, characterization and purification of additional interacting proteins or receptor proteins, or other signal transduction pathway proteins. Briefly, labeled polypeptide(s) of the invention is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, polypeptide of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as neural or liver cells, is passed over the column, and molecules with appropriate affinity bind to the polypeptides of the invention. The polypeptides of the invention - complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

Example 44: Assaying for Heparanase Activity

In order to assay for heparanase activity of the polypeptides of the invention, the heparanase assay described by Vlodavsky et al is utilized (Vlodavsky, I., et al., Nat. Med., 5:793-802 (1999)). Briefly, cell lysates, conditioned media or intact cells (1 x 10^6 cells per 35-mm dish) are incubated for 18 hrs at 37°C, pH 6.2-6.6, with ^{35}S-labeled ECM or soluble ECM derived peak I proteoglycans. The incubation medium is centrifuged and the supernatant is analyzed by gel filtration on a Sepharose CL-6B column (0.9 x 30 cm). Fractions are eluted with PBS and their radioactivity is measured. Degradation fragments of heparan sulfate side chains are eluted from Sepharose 6B at $0.5 < K_{av} < 0.8$ (peak II). Each experiment is done at least three times. Degradation fragments corresponding to "peak II," as described by Vlodavsky et al., is indicative of the activity of the polypeptides of the invention in cleaving heparan sulfate.

Example 45: Immobilization of biomolecules

This example provides a method for the stabilization of polypeptides of the invention in non-host cell lipid bilayer constucts (see, e.g., Bieri et al., Nature Biotech 17:1105-1108 (1999),

hereby incorporated by reference in its entirety herein) which can be adapted for the study of polypeptides of the invention in the various functional assays described above. Briefly, carbohydrate-specific chemistry for biotinylation is used to confine a biotin tag to the extracellular domain of the polypeptides of the invention, thus allowing uniform orientation upon immobilization. A 50uM solution of polypeptides of the invention in washed membranes is incubated with 20 mM NaIO4 and 1.5 mg/ml (4mM) BACH or 2 mg/ml (7.5mM) biotin-hydrazide for 1 hr at room temperature (reaction volume, 150ul). Then the sample is dialyzed (Pierce Slidealizer Cassett, 10 kDa cutoff; Pierce Chemical Co., Rockford IL) at 4C first for 5 h, exchanging the buffer after each hour, and finally for 12 h against 500 ml buffer R (0.15 M NaCl, 1 mM MgCl2, 10 mM sodium phosphate, pH7). Just before addition into a cuvette, the sample is diluted 1:5 in buffer ROG50 (Buffer R supplemented with 50 mM octylglucoside).

Example 46: TAQMAN

Quantitative PCR (QPCR). Total RNA from cells in culture are extracted by Trizol separation as recommended by the supplier (LifeTechnologies). (Total RNA is treated with DNase I (Life Technologies) to remove any contaminating genomic DNA before reverse transcription.) Total RNA (50 ng) is used in a one-step, 50ul, RT-QPCR, consisting of Taqman Buffer A (Perkin-Elmer; 50 mM KCl/10 mM Tris, pH 8.3), 5.5 mM $MgCl_2$, 240 μM each dNTP, 0.4 units RNase inhibitor(Promega), 8%glycerol, 0.012% Tween-20, 0.05% gelatin, 0.3uM primers, 0.1uM probe, 0.025units Amplitaq Gold (Perkin-Elmer) and 2.5 units Superscript II reverse transcriptase (Life Technologies). As a control for genomic contamination, parallel reactions are setup without reverse transcriptase. The relative abundance of (unknown) and 18S RNAs are assessed by using the Applied Biosystems Prism 7700 Sequence Detection System (Livak, K. J., Flood, S. J., Marmaro, J., Giusti, W. & Deetz, K. (1995) PCR Methods Appl. 4, 357-362). Reactions are carried out at 48°C for 30 min, 95°C for 10 min, followed by 40 cycles of 95°C for 15s, 60°C for 1 min. Reactions are performed in triplicate.

Primers (f & r) and FRET probes sets are designed using Primer Express Software (Perkin-Elmer). Probes are labeled at the 5'-end with the reporter dye 6-FAM and on the 3'-end with the quencher dye TAMRA (Biosource International, Camarillo, CA or Perkin-Elmer).

Example 47: Assays for Metalloproteinase Activity

Metalloproteinases (EC 3.4.24.-) are peptide hydrolases which use metal ions, such as Zn^{2+}, as the catalytic mechanism. Metalloproteinase activity of polypeptides of the present

invention can be assayed according to the following methods.

Proteolysis of alpha-2-macroglobulin

To confirm protease activity, purified polypeptides of the invention are mixed with the substrate alpha-2-macroglobulin (0.2 unit/ml; Boehringer Mannheim, Germany) in 1x assay buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM $CaCl_2$, 25 µM $ZnCl_2$ and 0.05% Brij-35) and incubated at 37°C for 1-5 days. Trypsin is used as positive control. Negative controls contain only alpha-2-macroglobulin in assay buffer. The samples are collected and boiled in SDS-PAGE sample buffer containing 5% 2-mercaptoethanol for 5-min, then loaded onto 8% SDS-polyacrylamide gel. After electrophoresis the proteins are visualized by silver staining. Proteolysis is evident by the appearance of lower molecular weight bands as compared to the negative control.

Inhibition of alpha-2-macroglobulin proteolysis by inhibitors of metalloproteinases

Known metalloproteinase inhibitors (metal chelators (EDTA, EGTA, AND $HgCl_2$), peptide metalloproteinase inhibitors (TIMP-1 and TIMP–2), and commercial small molecule MMP inhibitors) are used to characterize the proteolytic activity of polypeptides of the invention. The three synthetic MMP inhibitors used are: MMP inhibitor I, [IC_{50} = 1.0 µM against MMP-1 and MMP–8; IC_{50} = 30 µM against MMP-9; IC_{50} = 150 µM against MMP-3]; MMP-3 (stromelysin-1) inhibitor I [IC_{50} = 5 µM against MMP-3], and MMP-3 inhibitor II [K_i = 130 nM against MMP-3]; inhibitors available through Calbiochem, catalog # 444250, 444218, and 444225, respectively). Briefly, different concentrations of the small molecule MMP inhibitors are mixed with purified polypeptides of the invention (50µg/ml) in 22.9 µl of 1x HEPES buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM $CaCl_2$, 25 µM $ZnCl_2$ and 0.05%Brij-35) and incubated at room temperature (24 °C) for 2-hr, then 7.1 µl of substrate alpha-2-macroglobulin (0.2 unit/ml) is added and incubated at 37°C for 20-hr. The reactions are stopped by adding 4x sample buffer and boiled immediately for 5 minutes. After SDS-PAGE, the protein bands are visualized by silver stain.

Synthetic Fluorogenic Peptide Substrates Cleavage Assay

The substrate specificity for polypeptides of the invention with demonstrated metalloproteinase activity can be determined using synthetic fluorogenic peptide substrates (purchased from BACHEM Bioscience Inc). Test substrates include, M-1985, M-2225, M-2105, M-2110, and M-2255. The first four are MMP substrates and the last one is a substrate of tumor necrosis factor-α (TNF-α) converting enzyme (TACE). All the substrates are prepared in 1:1 dimethyl sulfoxide (DMSO) and water. The stock solutions are 50-500 µM. Fluorescent assays are performed by using a Perkin Elmer LS 50B luminescence spectrometer equipped with a constant

temperature water bath. The excitation λ is 328 nm and the emission λ is 393 nm. Briefly, the assay is carried out by incubating 176 µl 1x HEPES buffer (0.2 M NaCl, 10 mM $CaCl_2$, 0.05% Brij-35 and 50 mM HEPES, pH 7.5) with 4 µl of substrate solution (50 µM) at 25 °C for 15 minutes, and then adding 20 µl of a purified polypeptide of the invention into the assay cuvett. The final concentration of substrate is 1 µM. Initial hydrolysis rates are monitored for 30-min.

Example 48: Characterization of the cDNA contained in a deposited plasmid

The size of the cDNA insert contained in a deposited plasmid may be routinely determined using techniques known in the art, such as PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the cDNA sequence. For example, two primers of 17-30 nucleotides derived from each end of the cDNA (i.e., hybridizable to the absolute 5' nucleotide or the 3' nucleotide end of the sequence of SEQ ID NO:X, respectively) are synthesized and used to amplify the cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 ul of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 uM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

Incorporation by Reference

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. In addition, the sequence listing submitted herewith is incorporated herein by reference in its entirety. The specification and sequence listing of each of the following U.S. and PCT applications are herein incorporated by reference in their entirety: U.S. Appln. No. 60/040,162 filed on 07-Mar-1997, U.S. Appln. No. 60/043,576 filed on 11-Apr-1997, U.S. Appln. No. 60/047,601 filed on 23-May-1997, U.S. Appln. No. 60/056,845 filed on 22-Aug-1997, U.S. Appln. No. 60/043,580 filed on 11-Apr-1997, U.S. Appln. No. 60/047,599 filed on 23-May-1997, U.S. Appln. No. 60/056,664

filed on 22-Aug-1997, U.S. Appln. No. 60/043,314 filed on 11-Apr-1997, U.S. Appln. No. 60/047,632 filed on 23-May-1997, U.S. Appln. No. 60/056,892 filed on 22-Aug-1997, U.S. Appln. No. 60/043,568 filed on 11-Apr-1997, U.S. Appln. No. 60/047,595 filed on 23-May-1997, U.S. Appln. No. 60/056,632 filed on 22-Aug-1997, U.S. Appln. No. 60/043,578 filed on 11-Apr-1997, U.S. Appln. No. 60/040,333 filed on 07-Mar-1997, U.S. Appln. No. 60/043,670 filed on 11-Apr-1997, U.S. Appln. No. 60/047,596 filed on 23-May-1997, U.S. Appln. No. 60/056,864 filed on 22-Aug-1997, U.S. Appln. No. 60/043,674 filed on 11-Apr-1997, U.S. Appln. No. 60/047,612 filed on 23-May-1997, U.S. Appln. No. 60/056,631 filed on 22-Aug-1997, U.S. Appln. No. 60/043,569 filed on 11-Apr-1997, U.S. Appln. No. 60/047,588 filed on 23-May-1997, U.S. Appln. No. 60/056,876 filed on 22-Aug-1997, U.S. Appln. No. 60/043,671 filed on 11-Apr-1997, U.S. Appln. No. 60/043,311 filed on 11-Apr-1997, U.S. Appln. No. 60/038,621 filed on 07-Mar-1997, U.S. Appln. No. 60/043,672 filed on 11-Apr-1997, U.S. Appln. No. 60/047,613 filed on 23-May-1997, U.S. Appln. No. 60/056,636 filed on 22-Aug-1997, U.S. Appln. No. 60/043,669 filed on 11-Apr-1997, U.S. Appln. No. 60/047,582 filed on 23-May-1997, U.S. Appln. No. 60/056,910 filed on 22-Aug-1997, U.S. Appln. No. 60/043,315 filed on 11-Apr-1997, U.S. Appln. No. 60/047,598 filed on 23-May-1997, U.S. Appln. No. 60/056,874 filed on 22-Aug-1997, U.S. Appln. No. 60/043,312 filed on 11-Apr-1997, U.S. Appln. No. 60/047,585 filed on 23-May-1997, U.S. Appln. No. 60/056,881 filed on 22-Aug-1997, U.S. Appln. No. 60/043,313 filed on 11-Apr-1997, U.S. Appln. No. 60/047,586 filed on 23-May-1997, U.S. Appln. No. 60/056,909 filed on 22-Aug-1997, U.S. Appln. No. 60/040,161 filed on 07-Mar-1997, U.S. Appln. No. 60/047,587 filed on 23-May-1997, U.S. Appln. No. 60/056,879 filed on 22-Aug-1997, U.S. Appln. No. 60/047,500 filed on 23-May-1997, U.S. Appln. No. 60/056,880 filed on 22-Aug-1997, U.S. Appln. No. 60/047,584 filed on 23-May-1997, U.S. Appln. No. 60/056,894 filed on 22-Aug-1997, U.S. Appln. No. 60/047,492 filed on 23-May-1997, U.S. Appln. No. 60/056,911 filed on 22-Aug-1997, U.S. Appln. No. 60/040,626 filed on 07-Mar-1997, U.S. Appln. No. 60/047,503 filed on 23-May-1997, U.S. Appln. No. 60/056,903 filed on 22-Aug-1997, U.S. Appln. No. 60/047,501 filed on 23-May-1997, U.S. Appln. No. 60/056,637 filed on 22-Aug-1997, U.S. Appln. No. 60/047,590 filed on 23-May-1997, U.S. Appln. No. 60/056,875 filed on 22-Aug-1997, U.S. Appln. No. 60/047,581 filed on 23-May-1997, U.S. Appln. No. 60/056,882 filed on 22-Aug-1997, U.S. Appln. No. 60/047,592 filed on 23-May-1997, U.S. Appln. No. 60/056,888 filed on 22-Aug-1997, U.S. Appln. No. 60/040,334 filed on 07-Mar-1997, U.S. Appln. No. 60/047,618 filed on 23-May-1997, U.S. Appln. No. 60/056,872 filed on 22-Aug-1997, U.S. Appln. No. 60/047,617 filed on 23-May-1997, U.S. Appln. No. 60/056,662 filed on 22-Aug-1997, U.S. Appln. No. 60/047,589 filed on 23-May-1997, U.S. Appln. No. 60/056,862 filed on 22-Aug-1997, U.S. Appln. No. 60/047,594 filed on 23-May-1997, U.S. Appln. No. 60/056,884 filed on 22-Aug-1997, U.S. Appln. No. 60/047,583 filed on 23-May-1997, U.S.

Appln. No. 60/056,878 filed on 22-Aug-1997, U.S. Appln. No. 60/040,336 filed on 07-Mar-1997, U.S. Appln. No. 60/047,502 filed on 23-May-1997, U.S. Appln. No. 60/056,893 filed on 22-Aug-1997, U.S. Appln. No. 60/047,633 filed on 23-May-1997, U.S. Appln. No. 60/056,630 filed on 22-Aug-1997, U.S. Appln. No. 60/047,593 filed on 23-May-1997, U.S. Appln. No. 60/056,887 filed on 22-Aug-1997, U.S. Appln. No. 60/040,163 filed on 07-Mar-1997, U.S. Appln. No. 60/047,597 filed on 23-May-1997, U.S. Appln. No. 60/056,889 filed on 22-Aug-1997, U.S. Appln. No. 60/047,615 filed on 23-May-1997, U.S. Appln. No. 60/056,877 filed on 22-Aug-1997, U.S. Appln. No. 60/047,600 filed on 23-May-1997, U.S. Appln. No. 60/056,886 filed on 22-Aug-1997, U.S. Appln. No. 60/047,614 filed on 23-May-1997, U.S. Appln. No. 60/056,908 filed on 22-Aug-1997, U.S. Appln. No. 60/040,710 filed on 14-Mar-1997, U.S. Appln. No. 60/050,934 filed on 30-May-1997, U.S. Appln. No. 60/048,100 filed on 30-May-1997, U.S. Appln. No. 60/040,762 filed on 14-Mar-1997, U.S. Appln. No. 60/048,357 filed on 30-May-1997, U.S. Appln. No. 60/048,189 filed on 30-May-1997, U.S. Appln. No. 60/041,277 filed on 21-Mar-1997, U.S. Appln. No. 60/048,188 filed on 30-May-1997, U.S. Appln. No. 60/048,094 filed on 30-May-1997, U.S. Appln. No. 60/048,350 filed on 30-May-1997, U.S. Appln. No. 60/048,135 filed on 30-May-1997, U.S. Appln. No. 60/042,344 filed on 21-Mar-1997, U.S. Appln. No. 60/048,187 filed on 30-May-1997, U.S. Appln. No. 60/048,099 filed on 30-May-1997, U.S. Appln. No. 60/050,937 filed on 30-May-1997, U.S. Appln. No. 60/048,352 filed on 30-May-1997, U.S. Appln. No. 60/041,276 filed on 21-Mar-1997, U.S. Appln. No. 60/048,069 filed on 30-May-1997, U.S. Appln. No. 60/048,131 filed on 30-May-1997, U.S. Appln. No. 60/048,186 filed on 30-May-1997, U.S. Appln. No. 60/048,095 filed on 30-May-1997, U.S. Appln. No. 60/041,281 filed on 21-Mar-1997, U.S. Appln. No. 60/048,355 filed on 30-May-1997, U.S. Appln. No. 60/048,096 filed on 30-May-1997, U.S. Appln. No. 60/048,351 filed on 30-May-1997, U.S. Appln. No. 60/048,154 filed on 30-May-1997, U.S. Appln. No. 60/048,160 filed on 30-May-1997, U.S. Appln. No. 60/042,825 filed on 08-Apr-1997, U.S. Appln. No. 60/048,070 filed on 30-May-1997, U.S. Appln. No. 60/042,727 filed on 08-Apr-1997, U.S. Appln. No. 60/048,068 filed on 30-May-1997, U.S. Appln. No. 60/042,726 filed on 08-Apr-1997, U.S. Appln. No. 60/048,184 filed on 30-May-1997, U.S. Appln. No. 60/042,728 filed on 08-Apr-1997, U.S. Appln. No. 60/042,754 filed on 08-Apr-1997, U.S. Appln. No. 60/048,190 filed on 30-May-1997, U.S. Appln. No. 60/044,039 filed on 30-May-1997, U.S. Appln. No. 60/048,093 filed on 30-May-1997, U.S. Appln. No. 60/048,885 filed on 06-Jun-1997, U.S. Appln. No. 60/057,645 filed on 05-Sep-1997, U.S. Appln. No. 60/049,375 filed on 06-Jun-1997, U.S. Appln. No. 60/057,642 filed on 05-Sep-1997, U.S. Appln. No. 60/048,881 filed on 06-Jun-1997, U.S. Appln. No. 60/057,668 filed on 05-Sep-1997, U.S. Appln. No. 60/048,880 filed on 06-Jun-1997, U.S. Appln. No. 60/057,635 filed on 05-Sep-1997, U.S. Appln. No. 60/048,896 filed on 06-Jun-1997, U.S. Appln. No. 60/057,627 filed on 05-Sep-1997, U.S. Appln. No. 60/049,020

filed on 06-Jun-1997, U.S. Appln. No. 60/057,667 filed on 05-Sep-1997, U.S. Appln. No. 60/048,876 filed on 06-Jun-1997, U.S. Appln. No. 60/057,666 filed on 05-Sep-1997, U.S. Appln. No. 60/048,895 filed on 06-Jun-1997, U.S. Appln. No. 60/057,764 filed on 05-Sep-1997, U.S. Appln. No. 60/048,884 filed on 06-Jun-1997, U.S. Appln. No. 60/057,643 filed on 05-Sep-1997, U.S. Appln. No. 60/048,894 filed on 06-Jun-1997, U.S. Appln. No. 60/057,769 filed on 05-Sep-1997, U.S. Appln. No. 60/048,971 filed on 06-Jun-1997, U.S. Appln. No. 60/057,763 filed on 05-Sep-1997, U.S. Appln. No. 60/048,964 filed on 06-Jun-1997, U.S. Appln. No. 60/057,650 filed on 05-Sep-1997, U.S. Appln. No. 60/048,882 filed on 06-Jun-1997, U.S. Appln. No. 60/057,584 filed on 05-Sep-1997, U.S. Appln. No. 60/048,899 filed on 06-Jun-1997, U.S. Appln. No. 60/057,647 filed on 05-Sep-1997, U.S. Appln. No. 60/048,893 filed on 06-Jun-1997, U.S. Appln. No. 60/057,661 filed on 05-Sep-1997, U.S. Appln. No. 60/048,900 filed on 06-Jun-1997, U.S. Appln. No. 60/057,662 filed on 05-Sep-1997, U.S. Appln. No. 60/048,901 filed on 06-Jun-1997, U.S. Appln. No. 60/057,646 filed on 05-Sep-1997, U.S. Appln. No. 60/048,892 filed on 06-Jun-1997, U.S. Appln. No. 60/057,654 filed on 05-Sep-1997, U.S. Appln. No. 60/048,915 filed on 06-Jun-1997, U.S. Appln. No. 60/057,651 filed on 05-Sep-1997, U.S. Appln. No. 60/049,019 filed on 06-Jun-1997, U.S. Appln. No. 60/057,644 filed on 05-Sep-1997, U.S. Appln. No. 60/048,970 filed on 06-Jun-1997, U.S. Appln. No. 60/057,765 filed on 05-Sep-1997, U.S. Appln. No. 60/048,972 filed on 06-Jun-1997, U.S. Appln. No. 60/057,762 filed on 05-Sep-1997, U.S. Appln. No. 60/048,916 filed on 06-Jun-1997, U.S. Appln. No. 60/057,775 filed on 05-Sep-1997, U.S. Appln. No. 60/049,373 filed on 06-Jun-1997, U.S. Appln. No. 60/057,648 filed on 05-Sep-1997, U.S. Appln. No. 60/048,875 filed on 06-Jun-1997, U.S. Appln. No. 60/057,774 filed on 05-Sep-1997, U.S. Appln. No. 60/049,374 filed on 06-Jun-1997, U.S. Appln. No. 60/057,649 filed on 05-Sep-1997, U.S. Appln. No. 60/048,917 filed on 06-Jun-1997, U.S. Appln. No. 60/057,770 filed on 05-Sep-1997, U.S. Appln. No. 60/048,949 filed on 06-Jun-1997, U.S. Appln. No. 60/057,771 filed on 05-Sep-1997, U.S. Appln. No. 60/048,974 filed on 06-Jun-1997, U.S. Appln. No. 60/057,761 filed on 05-Sep-1997, U.S. Appln. No. 60/048,883 filed on 06-Jun-1997, U.S. Appln. No. 60/057,760 filed on 05-Sep-1997, U.S. Appln. No. 60/048,897 filed on 06-Jun-1997, U.S. Appln. No. 60/057,776 filed on 05-Sep-1997, U.S. Appln. No. 60/048,898 filed on 06-Jun-1997, U.S. Appln. No. 60/057,778 filed on 05-Sep-1997, U.S. Appln. No. 60/048,962 filed on 06-Jun-1997, U.S. Appln. No. 60/057,629 filed on 05-Sep-1997, U.S. Appln. No. 60/048,963 filed on 06-Jun-1997, U.S. Appln. No. 60/057,628 filed on 05-Sep-1997, U.S. Appln. No. 60/048,877 filed on 06-Jun-1997, U.S. Appln. No. 60/057,777 filed on 05-Sep-1997, U.S. Appln. No. 60/048,878 filed on 06-Jun-1997, U.S. Appln. No. 60/057,634 filed on 05-Sep-1997, U.S. Appln. No. 60/049,608 filed on 13-Jun-1997, U.S. Appln. No. 60/058,669 filed on 12-Sep-1997, U.S. Appln. No. 60/049,566 filed on 13-Jun-1997, U.S. Appln. No. 60/058,668 filed on 12-Sep-1997, U.S. Appln. No. 60/052,989 filed

on 13-Jun-1997, U.S. Appln. No. 60/058,750 filed on 12-Sep-1997, U.S. Appln. No. 60/049,607 filed on 13-Jun-1997, U.S. Appln. No. 60/058,665 filed on 12-Sep-1997, U.S. Appln. No. 60/049,611 filed on 13-Jun-1997, U.S. Appln. No. 60/058,971 filed on 12-Sep-1997, U.S. Appln. No. 60/050,901 filed on 13-Jun-1997, U.S. Appln. No. 60/058,972 filed on 12-Sep-1997, U.S. Appln. No. 60/049,609 filed on 13-Jun-1997, U.S. Appln. No. 60/058,975 filed on 12-Sep-1997, U.S. Appln. No. 60/048,356 filed on 30-May-1997, U.S. Appln. No. 60/056,296 filed on 29-Aug-1997, U.S. Appln. No. 60/048,101 filed on 30-May-1997, U.S. Appln. No. 60/056,293 filed on 29-Aug-1997, U.S. Appln. No. 60/050,935 filed on 30-May-1997, U.S. Appln. No. 60/056,250 filed on 29-Aug-1997, U.S. Appln. No. 60/049,610 filed on 13-Jun-1997, U.S. Appln. No. 60/061,060 filed on 02-Oct-1997, U.S. Appln. No. 60/049,606 filed on 13-Jun-1997, U.S. Appln. No. 60/060,841 filed on 02-Oct-1997, U.S. Appln. No. 60/049,550 filed on 13-Jun-1997, U.S. Appln. No. 60/060,834 filed on 02-Oct-1997, U.S. Appln. No. 60/049,549 filed on 13-Jun-1997, U.S. Appln. No. 60/060,865 filed on 02-Oct-1997, U.S. Appln. No. 60/049,548 filed on 13-Jun-1997, U.S. Appln. No. 60/060,844 filed on 02-Oct-1997, U.S. Appln. No. 60/049,547 filed on 13-Jun-1997, U.S. Appln. No. 60/061,059 filed on 02-Oct-1997, U.S. Appln. No. 60/051,381 filed on 01-Jul-1997, U.S. Appln. No. 60/058,598 filed on 12-Sep-1997, U.S. Appln. No. 60/051,480 filed on 01-Jul-1997, U.S. Appln. No. 60/058,663 filed on 12-Sep-1997, U.S. Appln. No. 60/051,926 filed on 08-Jul-1997, U.S. Appln. No. 60/058,785 filed on 12-Sep-1997, U.S. Appln. No. 60/052,793 filed on 08-Jul-1997, U.S. Appln. No. 60/058,664 filed on 12-Sep-1997, U.S. Appln. No. 60/051,925 filed on 08-Jul-1997, U.S. Appln. No. 60/058,660 filed on 12-Sep-1997, U.S. Appln. No. 60/051,929 filed on 08-Jul-1997, U.S. Appln. No. 60/058,661 filed on 12-Sep-1997, U.S. Appln. No. 60/052,803 filed on 08-Jul-1997, U.S. Appln. No. 60/055,722 filed on 18-Aug-1997, U.S. Appln. No. 60/052,732 filed on 08-Jul-1997, U.S. Appln. No. 60/055,723 filed on 18-Aug-1997, U.S. Appln. No. 60/051,932 filed on 08-Jul-1997, U.S. Appln. No. 60/055,948 filed on 18-Aug-1997, U.S. Appln. No. 60/051,931 filed on 08-Jul-1997, U.S. Appln. No. 60/055,949 filed on 18-Aug-1997, U.S. Appln. No. 60/051,916 filed on 08-Jul-1997, U.S. Appln. No. 60/055,953 filed on 18-Aug-1997, U.S. Appln. No. 60/051,930 filed on 08-Jul-1997, U.S. Appln. No. 60/055,950 filed on 18-Aug-1997, U.S. Appln. No. 60/051,918 filed on 08-Jul-1997, U.S. Appln. No. 60/055,947 filed on 18-Aug-1997, U.S. Appln. No. 60/051,920 filed on 08-Jul-1997, U.S. Appln. No. 60/055,964 filed on 18-Aug-1997, U.S. Appln. No. 60/052,733 filed on 08-Jul-1997, U.S. Appln. No. 60/056,360 filed on 18-Aug-1997, U.S. Appln. No. 60/052,795 filed on 08-Jul-1997, U.S. Appln. No. 60/055,684 filed on 18-Aug-1997, U.S. Appln. No. 60/051,919 filed on 08-Jul-1997, U.S. Appln. No. 60/055,984 filed on 18-Aug-1997, U.S. Appln. No. 60/051,928 filed on 08-Jul-1997, U.S. Appln. No. 60/055,954 filed on 18-Aug-1997, U.S. Appln. No. 60/052,870 filed on 16-Jul-1997, U.S. Appln. No. 60/055,952 filed on 18-Aug-1997, U.S. Appln. No. 60/052,871 filed

on 16-Jul-1997, U.S. Appln. No. 60/055,725 filed on 18-Aug-1997, U.S. Appln. No. 60/052,872 filed on 16-Jul-1997, U.S. Appln. No. 60/056,359 filed on 18-Aug-1997, U.S. Appln. No. 60/052,661 filed on 16-Jul-1997, U.S. Appln. No. 60/055,985 filed on 18-Aug-1997, U.S. Appln. No. 60/052,874 filed on 16-Jul-1997, U.S. Appln. No. 60/055,724 filed on 18-Aug-1997, U.S. Appln. No. 60/052,873 filed on 16-Jul-1997, U.S. Appln. No. 60/055,726 filed on 18-Aug-1997, U.S. Appln. No. 60/052,875 filed on 16-Jul-1997, U.S. Appln. No. 60/056,361 filed on 18-Aug-1997, U.S. Appln. No. 60/053,440 filed on 22-Jul-1997, U.S. Appln. No. 60/055,989 filed on 18-Aug-1997, U.S. Appln. No. 60/053,441 filed on 22-Jul-1997, U.S. Appln. No. 60/055,946 filed on 18-Aug-1997, U.S. Appln. No. 60/053,442 filed on 22-Jul-1997, U.S. Appln. No. 60/055,683 filed on 18-Aug-1997, U.S. Appln. No. 60/054,212 filed on 30-Jul-1997, U.S. Appln. No. 60/055,968 filed on 18-Aug-1997, U.S. Appln. No. 60/054,209 filed on 30-Jul-1997, U.S. Appln. No. 60/055,972 filed on 18-Aug-1997, U.S. Appln. No. 60/054,234 filed on 30-Jul-1997, U.S. Appln. No. 60/055,969 filed on 18-Aug-1997, U.S. Appln. No. 60/055,386 filed on 05-Aug-1997, U.S. Appln. No. 60/055,986 filed on 18-Aug-1997, U.S. Appln. No. 60/054,807 filed on 05-Aug-1997, U.S. Appln. No. 60/055,970 filed on 18-Aug-1997, U.S. Appln. No. 60/054,215 filed on 30-Jul-1997, U.S. Appln. No. 60/056,543 filed on 19-Aug-1997, U.S. Appln. No. 60/054,218 filed on 30-Jul-1997, U.S. Appln. No. 60/056,561 filed on 19-Aug-1997, U.S. Appln. No. 60/054,214 filed on 30-Jul-1997, U.S. Appln. No. 60/056,534 filed on 19-Aug-1997, U.S. Appln. No. 60/054,236 filed on 30-Jul-1997, U.S. Appln. No. 60/056,729 filed on 19-Aug-1997, U.S. Appln. No. 60/054,213 filed on 30-Jul-1997, U.S. Appln. No. 60/056,727 filed on 19-Aug-1997, U.S. Appln. No. 60/054,211 filed on 30-Jul-1997, U.S. Appln. No. 60/056,554 filed on 19-Aug-1997, U.S. Appln. No. 60/054,217 filed on 30-Jul-1997, U.S. Appln. No. 60/056,730 filed on 19-Aug-1997, U.S. Appln. No. 60/055,312 filed on 05-Aug-1997, U.S. Appln. No. 60/056,563 filed on 19-Aug-1997, U.S. Appln. No. 60/055,309 filed on 05-Aug-1997, U.S. Appln. No. 60/056,557 filed on 19-Aug-1997, U.S. Appln. No. 60/055,310 filed on 05-Aug-1997, U.S. Appln. No. 60/056,371 filed on 19-Aug-1997, U.S. Appln. No. 60/054,798 filed on 05-Aug-1997, U.S. Appln. No. 60/056,732 filed on 19-Aug-1997, U.S. Appln. No. 60/056,369 filed on 19-Aug-1997, U.S. Appln. No. 60/056,535 filed on 19-Aug-1997, U.S. Appln. No. 60/056,556 filed on 19-Aug-1997, U.S. Appln. No. 60/056,555 filed on 19-Aug-1997, U.S. Appln. No. 60/054,806 filed on 05-Aug-1997, U.S. Appln. No. 60/056,366 filed on 19-Aug-1997, U.S. Appln. No. 60/054,809 filed on 05-Aug-1997, U.S. Appln. No. 60/056,364 filed on 19-Aug-1997, U.S. Appln. No. 60/054,804 filed on 05-Aug-1997, U.S. Appln. No. 60/056,370 filed on 19-Aug-1997, U.S. Appln. No. 60/054,803 filed on 05-Aug-1997, U.S. Appln. No. 60/056,731 filed on 19-Aug-1997, U.S. Appln. No. 60/055,311 filed on 05-Aug-1997, U.S. Appln. No. 60/056,365 filed on 19-Aug-1997, U.S. Appln. No. 60/054,808 filed on 05-Aug-1997, U.S. Appln. No. 60/056,367 filed on 19-Aug-1997, U.S. Appln. No. 60/056,726

filed on 19-Aug-1997, U.S. Appln. No. 60/056,368 filed on 19-Aug-1997, U.S. Appln. No. 60/056,728 filed on 19-Aug-1997, U.S. Appln. No. 60/056,628 filed on 19-Aug-1997, U.S. Appln. No. 60/056,629 filed on 19-Aug-1997, U.S. Appln. No. 60/056,270 filed on 29-Aug-1997, U.S. Appln. No. 60/056,271 filed on 29-Aug-1997, U.S. Appln. No. 60/056,247 filed on 29-Aug-1997, U.S. Appln. No. 60/056,073 filed on 29-Aug-1997, U.S. Appln. No. 60/057,669 filed on 05-Sep-1997, U.S. Appln. No. 60/057,663 filed on 05-Sep-1997, U.S. Appln. No. 60/057,626 filed on 05-Sep-1997, U.S. Appln. No. 60/058,666 filed on 12-Sep-1997, U.S. Appln. No. 60/058,973 filed on 12-Sep-1997, U.S. Appln. No. 60/058,974 filed on 12-Sep-1997, U.S. Appln. No. 60/058,667 filed on 12-Sep-1997, U.S. Appln. No. 60/060,837 filed on 02-Oct-1997, U.S. Appln. No. 60/060,862 filed on 02-Oct-1997, U.S. Appln. No. 60/060,839 filed on 02-Oct-1997, U.S. Appln. No. 60/060,866 filed on 02-Oct-1997, U.S. Appln. No. 60/060,843 filed on 02-Oct-1997, U.S. Appln. No. 60/060,836 filed on 02-Oct-1997, U.S. Appln. No. 60/060,838 filed on 02-Oct-1997, U.S. Appln. No. 60/060,874 filed on 02-Oct-1997, U.S. Appln. No. 60/060,833 filed on 02-Oct-1997, U.S. Appln. No. 60/060,884 filed on 02-Oct-1997, U.S. Appln. No. 60/060,880 filed on 02-Oct-1997, U.S. Appln. No. 60/061,463 filed on 09-Oct-1997, U.S. Appln. No. 60/061,529 filed on 09-Oct-1997, U.S. Appln. No. 60/071,498 filed on 09-Oct-1997, U.S. Appln. No. 60/061,527 filed on 09-Oct-1997, U.S. Appln. No. 60/061,536 filed on 09-Oct-1997, U.S. Appln. No. 60/061,532 filed on 09-Oct-1997, U.S. Appln. No. 60/063,099 filed on 24-Oct-1997, U.S. Appln. No. 60/063,088 filed on 24-Oct-1997, U.S. Appln. No. 60/063,100 filed on 24-Oct-1997, U.S. Appln. No. 60/063,387 filed on 24-Oct-1997, U.S. Appln. No. 60/063,148 filed on 24-Oct-1997, U.S. Appln. No. 60/063,386 filed on 24-Oct-1997, U.S. Appln. No. 60/062,784 filed on 24-Oct-1997, U.S. Appln. No. 60/063,091 filed on 24-Oct-1997, U.S. Appln. No. 60/063,090 filed on 24-Oct-1997, U.S. Appln. No. 60/063,089 filed on 24-Oct-1997, U.S. Appln. No. 60/063,092 filed on 24-Oct-1997, U.S. Appln. No. 60/063,111 filed on 24-Oct-1997, U.S. Appln. No. 60/063,101 filed on 24-Oct-1997, U.S. Appln. No. 60/063,109 filed on 24-Oct-1997, U.S. Appln. No. 60/063,110 filed on 24-Oct-1997, U.S. Appln. No. 60/063,098 filed on 24-Oct-1997, U.S. Appln. No. 60/063,097 filed on 24-Oct-1997, U.S. Appln. No. 60/064,911 filed on 07-Nov-1997, U.S. Appln. No. 60/064,912 filed on 07-Nov-1997, U.S. Appln. No. 60/064,983 filed on 07-Nov-1997, U.S. Appln. No. 60/064,900 filed on 07-Nov-1997, U.S. Appln. No. 60/064,988 filed on 07-Nov-1997, U.S. Appln. No. 60/064,987 filed on 07-Nov-1997, U.S. Appln. No. 60/064,908 filed on 07-Nov-1997, U.S. Appln. No. 60/064,984 filed on 07-Nov-1997, U.S. Appln. No. 60/064,985 filed on 07-Nov-1997, U.S. Appln. No. 60/066,094 filed on 17-Nov-1997, U.S. Appln. No. 60/066,100 filed on 17-Nov-1997, U.S. Appln. No. 60/066,089 filed on 17-Nov-1997, U.S. Appln. No. 60/066,095 filed on 17-Nov-1997, U.S. Appln. No. 60/066,090 filed on 17-Nov-1997, U.S. Appln. No. 60/068,006 filed on 18-Dec-1997, U.S. Appln. No. 60/068,057 filed on 18-Dec-1997, U.S. Appln. No. 60/068,007

filed on 18-Dec-1997, U.S. Appln. No. 60/068,008 filed on 18-Dec-1997, U.S. Appln. No. 60/068,054 filed on 18-Dec-1997, U.S. Appln. No. 60/068,064 filed on 18-Dec-1997, U.S. Appln. No. 60/068,053 filed on 18-Dec-1997, U.S. Appln. No. 60/070,923 filed on 18-Dec-1997, U.S. Appln. No. 60/068,365 filed on 19-Dec-1997, U.S. Appln. No. 60/068,169 filed on 19-Dec-1997, U.S. Appln. No. 60/068,367 filed on 19-Dec-1997, U.S. Appln. No. 60/068,369 filed on 19-Dec-1997, U.S. Appln. No. 60/068,368 filed on 19-Dec-1997, U.S. Appln. No. 60/070,657 filed on 07-Jan-1998, U.S. Appln. No. 60/070,692 filed on 07-Jan-1998, U.S. Appln. No. 60/070,704 filed on 07-Jan-1998, U.S. Appln. No. 60/070,658 filed on 07-Jan-1998, U.S. Appln. No. 60/073,160 filed on 30-Jan-1998, U.S. Appln. No. 60/073,159 filed on 30-Jan-1998, U.S. Appln. No. 60/073,165 filed on 30-Jan-1998, U.S. Appln. No. 60/073,164 filed on 30-Jan-1998, U.S. Appln. No. 60/073,167 filed on 30-Jan-1998, U.S. Appln. No. 60/073,162 filed on 30-Jan-1998, U.S. Appln. No. 60/073,161 filed on 30-Jan-1998, U.S. Appln. No. 60/073,170 filed on 30-Jan-1998, U.S. Appln. No. 60/074,141 filed on 09-Feb-1998, U.S. Appln. No. 60/074,341 filed on 09-Feb-1998, U.S. Appln. No. 60/074,037 filed on 09-Feb-1998, U.S. Appln. No. 60/074,157 filed on 09-Feb-1998, U.S. Appln. No. 60/074,118 filed on 09-Feb-1998, U.S. Appln. No. 60/076,051 filed on 26-Feb-1998, U.S. Appln. No. 60/076,053 filed on 26-Feb-1998, U.S. Appln. No. 60/076,054 filed on 26-Feb-1998, U.S. Appln. No. 60/076,052 filed on 26-Feb-1998, U.S. Appln. No. 60/076,057 filed on 26-Feb-1998, U.S. Appln. No. 60/077,714 filed on 12-Mar-1998, U.S. Appln. No. 60/077,687 filed on 12-Mar-1998, U.S. Appln. No. 60/077,686 filed on 12-Mar-1998, U.S. Appln. No. 60/077,696 filed on 12-Mar-1998, U.S. Appln. No. 60/078,566 filed on 19-Mar-1998, U.S. Appln. No. 60/078,574 filed on 19-Mar-1998, U.S. Appln. No. 60/078,576 filed on 19-Mar-1998, U.S. Appln. No. 60/078,579 filed on 19-Mar-1998, U.S. Appln. No. 60/078,563 filed on 19-Mar-1998, U.S. Appln. No. 60/078,573 filed on 19-Mar-1998, U.S. Appln. No. 60/078,578 filed on 19-Mar-1998, U.S. Appln. No. 60/078,581 filed on 19-Mar-1998, U.S. Appln. No. 60/078,577 filed on 19-Mar-1998, U.S. Appln. No. 60/080,314 filed on 01-Apr-1998, U.S. Appln. No. 60/080,312 filed on 01-Apr-1998, U.S. Appln. No. 60/080,313 filed on 01-Apr-1998, U.S. Appln. No. 60/085,180 filed on 12-May-1998, U.S. Appln. No. 60/085,105 filed on 12-May-1998, U.S. Appln. No. 60/085,094 filed on 12-May-1998, U.S. Appln. No. 60/085,093 filed on 12-May-1998, U.S. Appln. No. 60/085,924 filed on 18-May-1998, U.S. Appln. No. 60/085,906 filed on 18-May-1998, U.S. Appln. No. 60/085,927 filed on 18-May-1998, U.S. Appln. No. 60/085,920 filed on 18-May-1998, U.S. Appln. No. 60/085,928 filed on 18-May-1998, U.S. Appln. No. 60/085,925 filed on 18-May-1998, U.S. Appln. No. 60/085,921 filed on 18-May-1998, U.S. Appln. No. 60/085,923 filed on 18-May-1998, U.S. Appln. No. 60/085,922 filed on 18-May-1998, U.S. Appln. No. 60/090,112 filed on 22-Jun-1998, U.S. Appln. No. 60/089,508 filed on 16-Jun-1998, U.S. Appln. No. 60/089,507 filed on 16-Jun-1998, U.S. Appln. No. 60/089,510 filed on 16-Jun-1998, U.S. Appln. No.

60/089,509 filed on 16-Jun-1998, U.S. Appln. No. 60/090,113 filed on 22-Jun-1998, U.S. Appln. No. 60/092,956 filed on 15-Jul-1998, U.S. Appln. No. 60/092,921 filed on 15-Jul-1998, U.S. Appln. No. 60/092,922 filed on 15-Jul-1998, U.S. Appln. No. 60/094,657 filed on 30-Jul-1998, U.S. Appln. No. 60/095,486 filed on 05-Aug-1998, U.S. Appln. No. 60/096,319 filed on 12-Aug-1998, U.S. Appln. No. 60/095,455 filed on 06-Aug-1998, U.S. Appln. No. 60/095,454 filed on 06-Aug-1998, U.S. Appln. No. 60/097,917 filed on 25-Aug-1998, U.S. Appln. No. 60/098,634 filed on 31-Aug-1998, U.S. Appln. No. 60/101,546 filed on 23-Sep-1998, U.S. Appln. No. 60/102,895 filed on 02-Oct-1998, U.S. Appln. No. 60/108,207 filed on 12-Nov-1998, U.S. Appln. No. 60/113,006 filed on 18-Dec-1998, U.S. Appln. No. 60/112,809 filed on 17-Dec-1998, U.S. Appln. No. 60/116,330 filed on 19-Jan-1999, U.S. Appln. No. 60/119,468 filed on 10-Feb-1999, U.S. Appln. No. 60/125,055 filed on 18-Mar-1999, U.S. Appln. No. 60/128,693 filed on 09-Apr-1999, U.S. Appln. No. 60/130,991 filed on 26-Apr-1999, U.S. Appln. No. 60/137,725 filed on 07-Jun-1999, U.S. Appln. No. 60/145,220 filed on 23-Jul-1999, U.S. Appln. No. 60/149,182 filed on 17-Aug-1999, U.S. Appln. No. 60/152,317 filed on 03-Sep-1999, U.S. Appln. No. 60/152,315 filed on 03-Sep-1999, U.S. Appln. No. 60/155,709 filed on 24-Sep-1999, U.S. Appln. No. 60/163,085 filed on 02-Nov-1999, U.S. Appln. No. 60/172,411 filed on 17-Dec-1999, U.S. Appln. No. 60/162,239 filed on 29-Oct-1999, U.S. Appln. No. 60/215,139 filed on 30-Jun-2000, U.S. Appln. No. 60/162,211 filed on 29-Oct-1999, U.S. Appln. No. 60/215,138 filed on 30-Jun-2000, U.S. Appln. No. 60/162,240 filed on 29-Oct-1999, U.S. Appln. No. 60/215,131 filed on 30-Jun-2000, U.S. Appln. No. 60/162,237 filed on 29-Oct-1999, U.S. Appln. No. 60/219,666 filed on 21-Jul-2000, U.S. Appln. No. 60/162,238 filed on 29-Oct-1999, U.S. Appln. No. 60/215,134 filed on 30-Jun-2000, U.S. Appln. No. 60/163,580 filed on 05-Nov-1999, U.S. Appln. No. 60/215,130 filed on 30-Jun-2000, U.S. Appln. No. 60/163,577 filed on 05-Nov-1999, U.S. Appln. No. 60/215,137 filed on 30-Jun-2000, U.S. Appln. No. 60/163,581 filed on 05-Nov-1999, U.S. Appln. No. 60/215,133 filed on 30-Jun-2000, U.S. Appln. No. 60/163,576 filed on 05-Nov-1999, U.S. Appln. No. 60/221,366 filed on 27-Jul-2000, U.S. Appln. No. 60/164,344 filed on 09-Nov-1999, U.S. Appln. No. 60/195,296 filed on 07-Apr-2000, U.S. Appln. No. 60/221,367 filed on 27-Jul-2000, U.S. Appln. No. 60/164,835 filed on 12-Nov-1999, U.S. Appln. No. 60/221,142 filed on 27-Jul-2000, U.S. Appln. No. 60/164,744 filed on 12-Nov-1999, U.S. Appln. No. 60/215,140 filed on 30-Jun-2000, U.S. Appln. No. 60/164,735 filed on 12-Nov-1999, U.S. Appln. No. 60/221,193 filed on 27-Jul-2000, U.S. Appln. No. 60/164,825 filed on 12-Nov-1999, U.S. Appln. No. 60/222,904 filed on 03-Aug-2000, U.S. Appln. No. 60/164,834 filed on 12-Nov-1999, U.S. Appln. No. 60/224,007 filed on 04-Aug-2000, U.S. Appln. No. 60/164,750 filed on 12-Nov-1999, U.S. Appln. No. 60/215,128 filed on 30-Jun-2000, U.S. Appln. No. 60/166,415 filed on 19-Nov-1999, U.S. Appln. No. 60/215,136 filed on 30-Jun-2000, U.S. Appln. No. 60/166,414 filed on 19-Nov-1999, U.S. Appln.

No. 60/219,665 filed on 21-Jul-2000, U.S. Appln. No. 60/164,731 filed on 12-Nov-1999, U.S. Appln. No. 60/215,132 filed on 30-Jun-2000, U.S. Appln. No. 60/226,280 filed on 18-Aug-2000, U.S. Appln. No. 60/256,968 filed on 21-Dec-2000, U.S. Appln. No. 60/226,380 filed on 18-Aug-2000, U.S. Appln. No. 60/259,803 filed on 05-Jan-2001, U.S. Appln. No. 60/228,084 filed on 28-Aug-2000, U.S. Appln. No. 09/915,582 filed on 27-Jul-2001, U.S. Appln. No. 60/231,968 filed on 12-Sep-2000, U.S. Appln. No. 60/236,326 filed on 29-Sep-2000, U.S. Appln. No. 60/234,211 filed on 20-Sep-2000, U.S. Appln. No. 60/226,282 filed on 18-Aug-2000, U.S. Appln. No. 60/232,104 filed on 12-Sep-2000, U.S. Appln. No. 60/234,210 filed on 20-Sep-2000, U.S. Appln. No. 60/226,278 filed on 18-Aug-2000, U.S. Appln. No. 60/259,805 filed on 05-Jan-2001, U.S. Appln. No. 60/226,279 filed on 18-Aug-2000, U.S. Appln. No. 60/259,678 filed on 05-Jan-2001, U.S. Appln. No. 60/226,281 filed on 18-Aug-2000, U.S. Appln. No. 60/231,969 filed on 12-Sep-2000, U.S. Appln. No. 60/228,086 filed on 28-Aug-2000, U.S. Appln. No. 60/259,516 filed on 04-Jan-2001, U.S. Appln. No. 60/228,083 filed on 28-Aug-2000, U.S. Appln. No. 60/259,804 filed on 05-Jan-2001, U.S. Appln. No. 60/270,658 filed on 23-Feb-2001, U.S. Appln. No. 60/304,444 filed on 12-Jul-2001, U.S. Appln. No. 60/270,625 filed on 23-Feb-2001, U.S. Appln. No. 60/304,417 filed on 12-Jul-2001, U.S. Appln. No. 60/295,869 filed on 06-Jun-2001, U.S. Appln. No. 60/304,121 filed on 11-Jul-2001, U.S. Appln. No. 60/311,085 filed on 10-Aug-2001, U.S. Appln. No. 60/325,209 filed on 28-Sep-2001, U.S. Appln. No. 60/330,629 filed on 26-Oct-2001, U.S. Appln. No. 60/331,046 filed on 07-Nov-2001, U.S. Appln. No. 60/358,554 filed on 22-Feb-2002, U.S. Appln. No. 60/358,714 filed on 25-Feb-2002, U.S. Appln. No. 60/277,340 filed on 21-Mar-2001, U.S. Appln. No. 60/306,171 filed on 19-Jul-2001, U.S. Appln. No. 60/278,650 filed on 27-Mar-2001, U.S. Appln. No. 60/331,287 filed on 13-Nov-2001, U.S. Appln. No. 09/950,082 filed on 12-Sep-2001, U.S. Appln. No. 09/950,083 filed on 12-Sep-2001, PCT Appln. No. US00/29363 filed on 25-Oct-2000, PCT Appln. No. US00/29360 filed on 25-Oct-2000, PCT Appln. No. US00/29362 filed on 25-Oct-2000, PCT Appln. No. US00/29365 filed on 25-Oct-2000, PCT Appln. No. US00/29364 filed on 25-Oct-2000, PCT Appln. No. US00/30040 filed on 01-Nov-2000, PCT Appln. No. US00/30037 filed on 01-Nov-2000, PCT Appln. No. US00/30045 filed on 01-Nov-2000, PCT Appln. No. US00/30036 filed on 01-Nov-2000, PCT Appln. No. US00/30039 filed on 01-Nov-2000, PCT Appln. No. US00/30654 filed on 08-Nov-2000, PCT Appln. No. US00/30628 filed on 08-Nov-2000, PCT Appln. No. US00/30653 filed on 08-Nov-2000, PCT Appln. No. US00/30629 filed on 08-Nov-2000, PCT Appln. No. US00/30679 filed on 08-Nov-2000, PCT Appln. No. US00/30674 filed on 08-Nov-2000, PCT Appln. No. US00/31162 filed on 15-Nov-2000, PCT Appln. No. US00/31282 filed on 15-Nov-2000, PCT Appln. No. US00/30657 filed on 08-Nov-2000, PCT Appln. No. US01/01396 filed on 17-Jan-2001, PCT Appln. No. US01/01387 filed on 17-Jan-2001, PCT Appln. No. US01/01567 filed on 17-Jan-2001, PCT

Appln. No. US01/01431 filed on 17-Jan-2001, PCT Appln. No. US01/01432 filed on 17-Jan-2001, PCT Appln. No. US01/00544 filed on 09-Jan-2001, PCT Appln. No. US01/01435 filed on 17-Jan-2001, PCT Appln. No. US01/01386 filed on 17-Jan-2001, PCT Appln. No. US01/01565 filed on 17-Jan-2001, PCT Appln. No. US01/01394 filed on 17-Jan-2001, PCT Appln. No. US01/01434 filed on 17-Jan-2001, PCT Appln. No. US01/01397 filed on 17-Jan-2001, PCT Appln. No. US01/01385 filed on 17-Jan-2001, PCT Appln. No. US01/01384 filed on 17-Jan-2001, PCT Appln. No. US01/01383 filed on 17-Jan-2001, PCT Appln. No. (Atty. Dkt. No. PS735; unassigned) filed on 21-Feb-2002, PCT Appln. No. (Atty. Dkt. No. PS736; unassigned) filed on 21-Feb-2002, U.S. Appln. No. 09/148,545 filed on 04-Sep-1998, U.S. Appln. No. 09/621,011 filed on 20-Jul-2000, U.S. Appln. No. 09/981,876 filed on 19-Oct-2001, U.S. Appln. No. 09/149,476 filed on 08-Sep-1998, U.S. Appln. No. 09/809,391 filed on 16-Mar-2001, U.S. Appln. No. 09/882,171 filed on 18-Jun-2001, U.S. Appln. No. 60/190,068 filed on 17-Mar-2000, U.S. Appln. No. 09/152,060 filed on 11-Sep-1998, U.S. Appln. No. 09/852,797 filed on 11-May-2001, U.S. Appln. No. 09/853,161 filed on 11-May-2001, U.S. Appln. No. 09/852,659 filed on 11-May-2001, U.S. Appln. No. 10/058,993 filed on 30-Jan-2002, U.S. Appln. No. 60/265,583 filed on 02-Feb-2001, U.S. Appln. No. 09/154,707 filed on 17-Sep-1998, U.S. Appln. No. 09/966,262 filed on 01-Oct-2001, U.S. Appln. No. 09/983,966 filed on 26-Oct-2001, U.S. Appln. No. 10/059,395 filed on 31-Jan-2002, U.S. Appln. No. 09/984,245 filed on 29-Oct-2001, U.S. Appln. No. 09/166,780 filed on 06-Oct-1998, U.S. Appln. No. 09/577,145 filed on 24-May-2000, U.S. Appln. No. 09/814,122 filed on 22-Mar-2001, U.S. Appln. No. 09/189,144 filed on 10-Nov-1998, U.S. Appln. No. 09/690,454 filed on 18-Oct-2000, U.S. Appln. No. (Atty. Dkt. No. PZ006G13A; unassigned) filed on 05-Feb-2002, U.S. Appln. No. 10/062,599 filed on 05-Feb-2002, U.S. Appln. No. 09/205,258 filed on 04-Dec-1998, U.S. Appln. No. 09/933,767 filed on 22-Aug-2001, U.S. Appln. No. 60/184,836 filed on 24-Feb-2000, U.S. Appln. No. 60/193,170 filed on 29-Mar-2000, U.S. Appln. No. 10/023,282 filed on 20-Dec-2001, U.S. Appln. No. 10/004,860 filed on 07-Dec-2001, U.S. Appln. No. 09/209,462 filed on 11-Dec-1998, U.S. Appln. No. 09/213,365 filed on 17-Dec-1998, U.S. Appln. No. 09/627,081 filed on 27-Jul-2000, U.S. Appln. No. 09/227,357 filed on 08-Jan-1999, U.S. Appln. No. 09/983,802 filed on 25-Oct-2001, U.S. Appln. No. 09/973,278 filed on 10-Oct-2001, U.S. Appln. No. 60/239,899 filed on 13-Oct-2000, U.S. Appln. No. 09/984,490 filed on 30-Oct-2001, U.S. Appln. No. 09/776,724 filed on 06-Feb-2001, U.S. Appln. No. 09/229,982 filed on 14-Jan-1999, U.S. Appln. No. 09/669,688 filed on 26-Sep-2000, U.S. Appln. No. 60/180,909 filed on 08-Feb-2000, U.S. Appln. No. 09/236,557 filed on 26-Jan-1999, U.S. Appln. No. 09/666,984 filed on 21-Sep-2000, U.S. Appln. No. 09/820,649 filed on 30-Mar-2001, U.S. Appln. No. 60/295,558 filed on 05-Jun-2001, U.S. Appln. No. 09/244,112 filed on 04-Feb-1999, U.S. Appln. No. 09/774,639 filed on 01-Feb-2001, U.S. Appln. No. 09/969,730 filed on 04-Oct-2001,

U.S. Appln. No. 60/238,291 filed on 06-Oct-2000, U.S. Appln. No. 09/251,329 filed on 17-Feb-1999, U.S. Appln. No. 09/716,128 filed on 17-Nov-2000, U.S. Appln. No. 09/257,179 filed on 25-Feb-1999, U.S. Appln. No. 09/729,835 filed on 06-Dec-2000, U.S. Appln. No. 09/262,109 filed on 04-Mar-1999, U.S. Appln. No. 09/722,329 filed on 28-Nov-2000, U.S. Appln. No. (Atty. Dkt. No. PZ016P1C1; unassigned) filed on 17-Jan-2002, U.S. Appln. No. 60/262,066 filed on 18-Jan-2001, U.S. Appln. No. 09/281,976 filed on 31-Mar-1999, U.S. Appln. No. 09/288,143 filed on 08-Apr-1999, U.S. Appln. No. 09/984,429 filed on 30-Oct-2001, U.S. Appln. No. 60/244,591 filed on 01-Nov-2000, U.S. Appln. No. 09/296,622 filed on 23-Apr-1999, U.S. Appln. No. 09/305,736 filed on 05-May-1999, U.S. Appln. No. 09/818,683 filed on 28-Mar-2001, U.S. Appln. No. 09/974,879 filed on 12-Oct-2001, U.S. Appln. No. 60/239,893 filed on 13-Oct-2000, U.S. Appln. No. 09/334,595 filed on 17-Jun-1999, U.S. Appln. No. 09/348,457 filed on 07-Jul-1999, U.S. Appln. No. 09/739,907 filed on 20-Dec-2000, U.S. Appln. No. 09/938,671 filed on 27-Aug-2001, U.S. Appln. No. 09/363,044 filed on 29-Jul-1999, U.S. Appln. No. 09/813,153 filed on 21-Mar-2001, U.S. Appln. No. 09/949,925 filed on 12-Sep-2001, U.S. Appln. No. 60/232,150 filed on 12-Sep-2000, U.S. Appln. No. 09/369,247 filed on 05-Aug-1999, U.S. Appln. No. 10/062,548 filed on 05-Feb-2002, U.S. Appln. No. 09/382,572 filed on 25-Aug-1999, U.S. Appln. No. 09/716,129 filed on 17-Nov-2000, U.S. Appln. No. 09/393,022 filed on 09-Sep-1999, U.S. Appln. No. 09/798,889 filed on 06-Mar-2001, U.S. Appln. No. 09/397,945 filed on 17-Sep-1999, U.S. Appln. No. 09/437,658 filed on 10-Nov-1999, U.S. Appln. No. 09/892,877 filed on 28-Jun-2001, U.S. Appln. No. 09/948,783 filed on 10-Sep-2001, U.S. Appln. No. 60/231,846 filed on 11-Sep-2000, U.S. Appln. No. 09/461,325 filed on 14-Dec-1999, U.S. Appln. No. 10/050,873 filed on 18-Jan-2002, U.S. Appln. No. 60/263,230 filed on 23-Jan-2001, U.S. Appln. No. 60/263,681 filed on 24-Jan-2001, U.S. Appln. No. 10/012,542 filed on 12-Dec-2001, U.S. Appln. No. 09/482,273 filed on 13-Jan-2000, U.S. Appln. No. 60/234,925 filed on 25-Sep-2000, U.S. Appln. No. 09/984,276 filed on 29-Oct-2001, U.S. Appln. No. 09/984,271 filed on 29-Oct-2001, U.S. Appln. No. 09/489,847 filed on 24-Jan-2000, U.S. Appln. No. 60/350,898 filed on 25-Jan-2002, U.S. Appln. No. 09/511,554 filed on 23-Feb-2000, U.S. Appln. No. 09/739,254 filed on 19-Dec-2000, U.S. Appln. No. 09/904,615 filed on 16-Jul-2001, U.S. Appln. No. 10/054,988 filed on 25-Jan-2002, U.S. Appln. No. 09/531,119 filed on 20-Mar-2000, U.S. Appln. No. 09/820,893 filed on 30-Mar-2001, U.S. Appln. No. 09/565,391 filed on 05-May-2000, U.S. Appln. No. 09/948,820 filed on 10-Sep-2001, U.S. Appln. No. 09/591,316 filed on 09-Jun-2000, U.S. Appln. No. 09/895,298 filed on 02-Jul-2001, U.S. Appln. No. 09/618,150 filed on 17-Jul-2000, U.S. Appln. No. 09/985,153 filed on 01-Nov-2001, U.S. Appln. No. 09/628,508 filed on 28-Jul-2000, U.S. Appln. No. 09/997,131 filed on 30-Nov-2001, U.S. Appln. No. 09/661,453 filed on 13-Sep-2000, U.S. Appln. No. 10/050,882 filed on 18-Jan-2002, U.S. Appln. No. 09/684,524 filed on 10-Oct-2000, U.S. Appln. No.

10/050,704 filed on 18-Jan-2002, U.S. Appln. No. 09/726,643 filed on 01-Dec-2000, U.S. Appln. No. 10/042,141 filed on 11-Jan-2002, U.S. Appln. No. 09/756,168 filed on 09-Jan-2001, U.S. Appln. No. 09/781,417 filed on 13-Feb-2001, U.S. Appln. No. (Atty. Dkt. No. PZ042P1C1; unassigned) filed on 01-Feb-2002, U.S. Appln. No. 09/789,561 filed on 22-Feb-2001, U.S. Appln. No. 09/800,729 filed on 08-Mar-2001, U.S. Appln. No. 09/832,129 filed on 11-Apr-2001, PCT Appln. No.US98/04482 filed on 06-Mar-1998, PCT Appln. No.US98/04493 filed on 06-Mar-1998, PCT Appln. No.US98/04858 filed on 12-Mar-1998, PCT Appln. No.US98/05311 filed on 19-Mar-1998, PCT Appln. No.US98/06801 filed on 07-Apr-1998, PCT Appln. No.US98/10868 filed on 28-May-1998, PCT Appln. No.US98/11422 filed on 04-Jun-1998, PCT Appln. No.US01/05614 filed on 21-Feb-2001, PCT Appln. No.US98/12125 filed on 11-Jun-1998, PCT Appln. No.US98/13608 filed on 30-Jun-1998, PCT Appln. No.US98/13684 filed on 07-Jul-1998, PCT Appln. No.US98/14613 filed on 15-Jul-1998, PCT Appln. No.US98/15949 filed on 29-Jul-1998, PCT Appln. No.US98/16235 filed on 04-Aug-1998, PCT Appln. No.US98/17044 filed on 18-Aug-1998, PCT Appln. No.US98/17709 filed on 27-Aug-1998, PCT Appln. No.US98/18360 filed on 03-Sep-1998, PCT Appln. No.(Atty. Dkt. No. PZ016PCT2; unassigned) filed on 17-Jan-2002, PCT Appln. No.US98/20775 filed on 01-Oct-1998, PCT Appln. No.US98/21142 filed on 08-Oct-1998, PCT Appln. No.US98/22376 filed on 23-Oct-1998, PCT Appln. No.US98/23435 filed on 04-Nov-1998, PCT Appln. No.US98/27059 filed on 17-Dec-1998, PCT Appln. No.US99/00108 filed on 06-Jan-1999, PCT Appln. No.US99/01621 filed on 27-Jan-1999, PCT Appln. No.US99/02293 filed on 04-Feb-1999, PCT Appln. No.US99/03939 filed on 24-Feb-1999, PCT Appln. No.US99/05721 filed on 11-Mar-1999, PCT Appln. No.US99/05804 filed on 18-Mar-1999, PCT Appln. No.US99/09847 filed on 06-May-1999, PCT Appln. No.US99/13418 filed on 15-Jun-1999, PCT Appln. No.US99/15849 filed on 14-Jul-1999, PCT Appln. No.US01/00911 filed on 12-Jan-2001, PCT Appln. No.US01/29871 filed on 24-Sep-2001, PCT Appln. No.US99/17130 filed on 29-Jul-1999, PCT Appln. No.US99/19330 filed on 24-Aug-1999, PCT Appln. No.US99/22012 filed on 22-Sep-1999, PCT Appln. No.US99/26409 filed on 09-Nov-1999, PCT Appln. No.US99/29950 filed on 16-Dec-1999, PCT Appln. No.US00/00903 filed on 18-Jan-2000, PCT Appln. No.US00/03062 filed on 08-Feb-2000, PCT Appln. No.US00/06783 filed on 16-Mar-2000, PCT Appln. No.US00/08979 filed on 06-Apr-2000, PCT Appln. No.US00/15187 filed on 02-Jun-2000, PCT Appln. No.US00/19735 filed on 20-Jul-2000, PCT Appln. No.US00/22325 filed on 16-Aug-2000, PCT Appln. No.US00/24008 filed on 31-Aug-2000, PCT Appln. No.US00/26013 filed on 22-Sep-2000, PCT Appln. No.US00/28664 filed on 17-Oct-2000, US Appln. No. 09/833,245 filed on 12-Apr-2001, and PCT Appln. No. US01/11988 filed on 12-Apr-2001.

Applicant's File Reference Number: PS906PCT	International Application Number: Unassigned

INDICATIONS RELATING TO DEPOSITED BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited biological material referred to in Table 1A of the description.

B. IDENTIFICATION OF DEPOSIT:

Further deposits are identified on an additional sheet: X

Name of Depository: **American Type Culture Collection**
Address of Depository: **10801 University Boulevard**
Manassas, Virginia 20110-2209
United States of America

	Accession Number	Date of Deposit		Accession Number	Date of Deposit
1	203027	26-Jun-1998	2	209463	14-Nov-1997
3	203069	27-Jul-1998	4	209551	12-Dec-1997
5	203070	27-Jul-1998	6	209563	18-Dec-1997
7	203071	27-Jul-1998	8	209580	14-Jan-1998
9	203331	8-Oct-1998	10	209603	29-Jan-1998
11	203364	19-Oct-1998	12	209626	12-Feb-1998
13	203499	1-Dec-1998	14	209627	12-Feb-1998
15	203517	10-Dec-1998	16	209628	12-Feb-1998
17	203570	11-Jan-1999	18	209641	25-Feb-1998
19	203648	9-Feb-1999	20	209651	4-Mar-1998
21	209007	28-Apr-1997	22	209683	20-Mar-1998
23	209008	28-Apr-1997	24	209745	7-Apr-1998
25	209010	28-Apr-1997	26	209746	7-Apr-1998
27	209012	28-Apr-1997	28	209782	20-Apr-1998
29	209045	15-May-1997	30	209852	7-May-1998
31	209070	22-May-1997	32	209877	18-May-1998
33	209071	22-May-1997	34	209878	18-May-1998
35	209072	22-May-1997	36	209889	22-May-1998
37	209082	29-May-1997	38	209965	11-Jun-1998
39	209083	29-May-1997	40	97899	26-Feb-1997
41	209084	29-May-1997	42	97922	7-Mar-1997
43	209085	29-May-1997	44	97923	7-Mar-1997
45	209089	5-Jun-1997	46	97958	13-Mar-1997
47	209119	12-Jun-1997	48	97977	4-Apr-1997
49	209125	19-Jun-1997	50	PTA-1543	21-Mar-2000
51	209126	19-Jun-1997	52	PTA-1544	21-Mar-2000
53	209138	3-Jul-1997	54	PTA-163	1-Jun-1999
55	209139	3-Jul-1997	56	PTA-2069	9-Jun-2000
57	209145	17-Jul-1997	58	PTA-2075	9-Jun-2000
59	209195	1-Aug-1997	60	PTA-2076	9-Jun-2000
61	209215	21-Aug-1997	62	PTA-322	9-Jul-1999
63	209224	28-Aug-1997	64	PTA-622	2-Sep-1999

Applicant's File Reference Number: PS906PCT	International Application Number: Unassigned

	Accession Number	Date of Deposit		Accession Number	Date of Deposit
65	209225	28-Aug-1997	66	PTA-623	2-Sep-1999
67	209236	4-Sep-1997	68	PTA-841	13-Oct-1999
69	209242	12-Sep-1997	70	PTA-842	13-Oct-1999
71	209243	12-Sep-1997	72	PTA-843	13-Oct-1999
73	209244	12-Sep-1997	74	PTA-845	13-Oct-1999
75	209277	18-Sep-1997	76	PTA-847	13-Oct-1999
77	209299	25-Sep-1997	78	PTA-848	13-Oct-1999
79	209300	25-Sep-1997	80	PTA-849	13-Oct-1999
81	209324	2-Oct-1997	82	PTA-855	18-Oct-1999
83	209346	9-Oct-1997	84	PTA-867	26-Oct-1999
85	209368	16-Oct-1997	86	PTA-868	26-Oct-1999
87	209407	23-Oct-1997	88	PTA-871	26-Oct-1999
89	209423	30-Oct-1997	90	PTA-885	28-Oct-1999

EUROPE

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

What Is Claimed Is:

1. Use of a polypeptide for the preparation of a diagnostic or pharmaceutical composition for diagnosing or treating a gastrointestinal disorder, wherein said polypeptide comprises an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(b) a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(e) a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(f) a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(g) a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

2. Use of the polypeptide of claim 1, wherein said wherein said polypeptide comprises a heterologous amino acid sequence.

3. Use of a polypeptide for the preparation of a diagnostic or pharmaceutical composition for diagnosing or treating a gastrointestinal disorder, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of:

(a) a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(b) a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(e) a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(f) a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(g) a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

4. Use of the polypeptide of claim 3, wherein said polypeptide comprises a heterologous amino acid sequence.

5. Use of an antibody or fragment thereof for the preparation of a diagnostic or pharmaceutical composition for diagnosing or treating a gastrointestinal disorder, wherein said antibody or fragment thereof binds a polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(b) a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(e) a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(f) a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(g) a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

6. Use of an antibody or fragment thereof for the preparation of a diagnostic or pharmaceutical composition for diagnosing or treating a gastrointestinal disorder, wherein said antibody or fragment thereof binds a polypeptide selected from the group consisting of:

(a) a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(b) a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(e) a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(f) a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(g) a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

7. Use of a nucleic acid molecule for the preparation of a diagnostic or pharmaceutical composition for diagnosing or treating a gastrointestinal disorder, wherein said nucleic acid molecule comprises a polynucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X as referenced in Table 1A;

(b) a polynucleotide encoding a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polynucleotide encoding a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(e) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(f) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(g) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(h) a polynucleotide encoding a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

8. Use of the nucleic acid molecule of claim 7, wherein said nucleic acid molecule comprises a heterologous polynucleotide sequence.

9. Use of a nucleic acid molecule for the preparation of a diagnostic or pharmaceutical composition for diagnosing or treating a gastrointestinal disorder, wherein said nucleic acid molecule comprises a polynucleotide sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X as referenced in Table 1A;

(b) a polynucleotide encoding a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polynucleotide encoding a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(e) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(f) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(g) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(h) a polynucleotide encoding a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

10. Use of the nucleic acid molecule of claim 9, wherein said nucleic acid molecule comprises a heterologous polynucleotide sequence.

11. Use of an agonist or antagonist for the preparation of a pharmaceutical composition for treating a gastrointestinal disorder, wherein said agonist or antagonist binds a polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(b) a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(e) a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(f) a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(g) a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

12. Use of an agonist or antagonist for the preparation of a pharmaceutical composition for treating a gastrointestinal disorder, wherein said agonist or antagonist binds a polypeptide selected from the group consisting of:

(a) a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(b) a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(e) a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(f) a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(g) a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

13. A polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(b) a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(e) a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(f) a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(g) a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

14. The polypeptide of claim 13, wherein said polypeptide comprises a heterologous amino acid sequence.

15. Use of the polypeptide of claim 13 for identifying a binding partner comprising:

(a) contacting the polypeptide of claim 13 with a binding partner; and

(b) determining whether the binding partner increases or decreases activity of the polypeptide.

16. A polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(b) a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(e) a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(f) a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(g) a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

17. The polypeptide of claim 16, wherein said polypeptide comprises a heterologous polypeptide sequence.

18. Use of the polypeptide of claim 16 for identifying a binding partner comprising:

(a) contacting the polypeptide of claim 16 with a binding partner; and

(b) determining whether the binding partner increases or decreases activity of the polypeptide.

19. An antibody or fragment thereof that binds a polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(b) a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(e) a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(f) a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(g) a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

20.An antibody or fragment thereof that binds a polypeptide selected from the group consisting of:

(a) a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(b) a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(e) a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(f) a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(g) a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

21. A nucleic acid molecule comprising a polynucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X as referenced in Table 1A;

(b) a polynucleotide encoding a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polynucleotide encoding a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(e) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(f) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(g) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(h) a polynucleotide encoding a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

22. The nucleic acid molecule of claim 21, wherein said nucleic acid molecule comprises a heterologous polynucleotide sequence.

23. A recombinant vector comprising the nucleic acid molecule of claim 21.

24. A recombinant vector comprising the nucleic acid molecule of claim 22.

25. A recombinant host cell comprising the recombinant vector of claim 23.

26. A recombinant host cell comprising the recombinant vector of claim 24.

27. A nucleic acid molecule comprising a polynucleotide sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X as referenced in Table 1A;

(b) a polynucleotide encoding a full length polypeptide of SEQ ID NO:Y or a full length polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(c) a polynucleotide encoding a predicted secreted form of SEQ ID NO:Y or a secreted form of the polypeptide encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(d) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A;

(e) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA Clone ID in ATCC Deposit No:Z corresponding to SEQ ID NO:Y as referenced in Table 1A, wherein said fragment has biological activity;

(f) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y as referenced in Table 1B;

(g) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y as referenced in Table 2; and

(h) a polynucleotide encoding a predicted epitope of SEQ ID NO:Y as referenced in Table 1B.

28. The nucleic acid molecule of claim 27, wherein said nucleic acid molecule comprises a heterologous polynucleotide sequence.

29. A recombinant vector comprising the nucleic acid molecule of claim 27.

30. A recombinant vector comprising the nucleic acid molecule of claim 28.

31. A recombinant host cell comprising the recombinant vector of claim 29.

32. A recombinant host cell comprising the recombinant vector of claim 30.

Sequence List

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<212> DNA
<213> Homo sapiens

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<220>
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<223> n equals a,t,g, or c

<220>
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<222> (1319)..(1319)
<223> n equals a,t,g, or c

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aaaaaaaaaa aaa 1333

<210> 15
<211> 751
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

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atcatacagg ctcctcatct acaaagttcc agtagcagtg acgcctacac ggaagacttg 660
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<210> 16
<211> 2849
<212> DNA
<213> Homo sapiens

<220>

<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

<400> 16
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ctgaggttag ccctgcggcc gtgtgcccgc gcctctcccg ccgggccgcg cgcctatcac     180
ggggactcgg tggcctcgct gggcacccag ccggacttgg gctctgccct ctaccaggag     240
aactacaagc agatgaaagc actagtaaat cagctccatg aacgagtgga gcatataaaa     300
ctaggaggtg gtgagaaagc ccgagcactt cacatatcaa gaggaaaact attgcccaga     360
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ggttaccagt tatatgacaa tgaggaggtg ccaggaggtg gcattattac aggcattgga     480
agagtatcag gagtagaatg catgattatt gccaatgatg ccaccgtcaa aggaggtgcc     540
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<210> 17
<211> 755
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature

<222> (1)..(1)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (733)..(734)
<223> n equals a,t,g, or c

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<210> 18
<211> 4129
<212> DNA
<213> Homo sapiens

<400> 18
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<210> 19
<211> 1674
<212> DNA
<213> Homo sapiens

<220>
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<222> (1649)..(1649)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1663)..(1663)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1665)..(1665)
<223> n equals a,t,g, or c

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<210> 20
<211> 2005
<212> DNA
<213> Homo sapiens

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ttgaaaatta ttaccatatg tttagagcaa atccaagaaa acttcaacag cttctgaaga   1920
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<210> 21
<211> 812
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (17)..(17)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (108)..(108)
<223> n equals a,t,g, or c

<400> 21

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gagaggactt ccccacctca tgcagctatt tgggccgtgg cgtctgaaat ttattatttc    180
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<210> 22
<211> 910
<212> DNA
<213> Homo sapiens

<400> 22

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atcggggccc tgggaagcgc ctgtctatcc cgggggcagg acctgagcgc ccctgaccct    180
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<210> 23
<211> 821
<212> DNA
<213> Homo sapiens

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tcatgtgtat gaactccacc ttatgtgtag tcttatccct cacccactcc tgcccttccc 480
cacaagtccc caaagtccat tatatgatct ttatgccttt acatcttcac agtttagctc 540
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taatttaaga aaccttatgc aagtaattat tagtcatcat cccaaaaaaa agggagaaca 660
gggttagatt cagaatactt tgataagagc taaatactat catgagtgct gtcagtctgt 720
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<210> 24
<211> 981
<212> DNA
<213> Homo sapiens

<400> 24
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aaaaagcttt tttgcccaaa a 981

<210> 25
<211> 1038
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2)..(2)
<223> n equals a,t,g, or c

<400> 25
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taaatggcag ctgacagcat gaaaataaca tatctaatat tttgtgacta tcttattagg 240
aaaatcagag aatttcaaaa ccttgttagt ttttagggta tagtcacatt ttataaatgt 300

gcggtatatt tatacatgat ttgacgtttg tgwaaatatt ttccctggac ttttatttta 360
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<210> 26
<211> 843
<212> DNA
<213> Homo sapiens

<400> 26
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tcacaacagg gagccccca gtccctgagg cccacagccc tggatttgac ggggccagct 480
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<210> 27
<211> 601
<212> DNA
<213> Homo sapiens

<400> 27
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<210> 28
<211> 1276
<212> DNA
<213> Homo sapiens

<400> 28
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<210> 29
<211> 2084
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2075)..(2075)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2083)..(2083)
<223> n equals a,t,g, or c

<400> 29

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<210> 30
<211> 1765
<212> DNA
<213> Homo sapiens

<400> 30
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<210> 31
<211> 2494
<212> DNA
<213> Homo sapiens

<400> 31
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<210> 32
<211> 885
<212> DNA
<213> Homo sapiens

<220>
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<222> (233)..(233)
<223> n equals a,t,g, or c

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tacaaccacc ccagcaggtc tccagttcct gccaggttag tgtggatggc ccagcaccat 180
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acacagggtg gggaacatca cacaccgggg cctgtcgtgg ggtgaggggg atggggcagg 720

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atggcacatg tatacatatg taacaaacct gcatgttgtg cacatgtacc ccagaactta     840
aagtataata aattaaaatt aaaaaaaaaa aaaaaaaact cgtag                     885

<210> 33
<211> 790
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (37)..(37)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (55)..(55)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (76)..(76)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (112)..(112)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (120)..(120)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (137)..(137)
<223> n equals a,t,g, or c

<400> 33
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cagtgagcgc aacgcantta aatgtgagtt agctcactca ttagcacccc aggctttaca     180
ctttatgctt ccggctcgta tgttgtgtgg aattgtgagc ggataacaat ttcacacagg     240
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acgcctgcag gtaccggtcc ggaattcccg ggtcgaccca cgcgtccggt tgaatgcact     360
gagtcccttg gtgtagtagc aataaggaaa aatgaaatta ctttcctgtg cacacagtcc     420
agcctaattg gtatgtgatg ttgcacttag cagccatgtg gtgggcatgt gtgactactc     480
tggttttcac tttagtttct aaacttttta tccctctcaa gtccagcatg gatggggaaa     540
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ttgtgtcctg ctttgagctg taccttgtcc agtccattgt gaaattatcc cagcagctgt     660
aatgtacagt tccttctgaa gcaagcaaca tcagcagcag cagcagcagc agcacaattc     720
tgtgttttat aaagacaaca gtggcttcta wwaaaaaaaa aaaaaaaaaa aaaaaaaaaa     780
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<210> 34
<211> 1343
<212> DNA
<213> Homo sapiens

<400> 34
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gcctctggtt ctgggtgagg ttatttgcag gtggagacgg ggggctgcac ctgaacattt    180
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gccacctttc atggaagggg agatttatgg gctttcctgg aacccccagg ctgtcctggc    360
caagaggaaa gaggtggtta cttcaggagt ttgaccttag ttagataact aaaagaatac    420
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ttttgaaaaa aaaaaaaaaa aaa                                            1343
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<210> 35
<211> 1089
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (353)..(353)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (528)..(528)
<223> n equals a,t,g, or c

<400> 35

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ctctactcgt gcggtgcttc ttctccttgg catacagctc acagctcttt ggcctatagc    180
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tcgtcctcta gacgggggac ctgagcagtt tgtattctac taccacatag atnccttcca    360
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gatcataata gtaattgtag tggtcctctt ccagcattac cggaaaaagc gatgggccga    660
aagagctcat aaagtggtgg agataaaatc aaaagaagag gaaaggctca accaagagaa    720
aaaggtctct gtttatttag aagacacaga ctaacaattt tagatggtaa ggttcacaaa    780
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gagacaaaag tcttctatta gtcttatgga tagctcctcc ttgagtgtat tttgtgcaaa    960
agattaagaa gctggactct actgccatta aagctgagag aatcctaagg ttaaaaaaaa   1020
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<210> 36

<211> 875
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (66)..(66)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (872)..(872)
<223> n equals a,t,g, or c

<400> 36
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ggcaggaagc cgtgtctgca gaggctcctc cctgcctcag gtggccccgt tcaaccccag 180
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<210> 37
<211> 320
<212> DNA
<213> Homo sapiens

<400> 37
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carrgccatg ctgtcgaggg cttcctgcaa ttgcagrcgt gcttcgccgr cttgttcgtg 180
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gcgcgcttcg tcctgcaaca 320

<210> 38
<211> 710
<212> DNA
<213> Homo sapiens

<400> 38
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<210> 39
<211> 1421
<212> DNA
<213> Homo sapiens

<400> 39
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<210> 40
<211> 3447
<212> DNA
<213> Homo sapiens

<400> 40
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<212> DNA
<213> Homo sapiens

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<211> 767
<212> DNA
<213> Homo sapiens

<400> 42
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<210> 43
<211> 1057
<212> DNA
<213> Homo sapiens

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<210> 44
<211> 2687
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1614)..(1614)
<223> n equals a,t,g, or c

<400> 44

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cccagtggtg ctggtccctg gtgatttggg taaccaactg gaagccaagc tggacaagcc    180
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<210> 45
<211> 728
<212> DNA
<213> Homo sapiens

<400> 45

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taaattatgt atacataata tataaccaaa ttgaaacagt tttacaattt ggtttgactg    660
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<210> 46
<211> 1635
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (85)..(85)
<223> n equals a,t,g, or c

<400> 46

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<211> 4893
<212> DNA
<213> Homo sapiens

<400> 47
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<212> DNA
<213> Homo sapiens

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<211> 1748
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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ctttatcatt agatatgacg tcaatagaga acagagcatt ggggacatcc aggttctaaa    240
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caaccggatc aaagtatgga aggaccactt gatatcagtc actccagaca gcatcaggga     480
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gcagagggcc atcaggctcc tcaacaagta cgtggcccac agtggcattg gagaccggag     600
cgtgtccctc atcgtcttcc tgacggatgg gaagcccacg gtcggggaga cgcacaccct     660
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<210> 58
<211> 2207
<212> DNA
<213> Homo sapiens

<400> 58

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catttgaggt tatgttctat aagttaacgt tgatcttgtg tgagctttcg gtagctggag     180
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<210> 59
<211> 3533
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (44)..(44)
<223> n equals a,t,g, or c

<400> 59
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gtaattacaa aaaagtgaag agtttacaga tatacaagga aataaaggcg aattattgca    180
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<210> 60
<211> 867
<212> DNA
<213> Homo sapiens

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<211> 1558
<212> DNA
<213> Homo sapiens

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cactcttcca aggtcttggc ttgaacccaa ttttttttga gagaataaac caggcttttt 600
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<211> 2199
<212> DNA
<213> Homo sapiens

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<211> 832
<212> DNA
<213> Homo sapiens

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<222> (827)..(829)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (831)..(831)
<223> n equals a,t,g, or c

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<210> 64
<211> 1336
<212> DNA
<213> Homo sapiens

<400> 64
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caggcaagac cagctgaaag aggttccgca actgtgtcat ttggagagct aggaaaaata 1260
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<210> 65
<211> 799
<212> DNA
<213> Homo sapiens

<400> 65
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ttcctgggat tggcagaagc ctgtactcct cgtgaagtca acttgctgaa agggatcata 180
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aggaaaccac tccccaagag gaagaacacg tggaacttcc tgaaatgcgc ctacatggtg 360
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<210> 66
<211> 1347
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (83)..(83)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (334)..(334)
<223> n equals a,t,g, or c

<400> 66
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tttgggcggc ccctgctgct gtcggccctg cacatgctgg tggcagccct ggcatgccac 180
cggggggcac ggcgccccat gccaggcggc actcgctgcc gagtcctact gctcagtctc 240
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aaaaaaaaaa aaaaaaccgg cacgtag 1347

<210> 67
<211> 642
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (41)..(41)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (49)..(49)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (64)..(64)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (607)..(607)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (621)..(621)
<223> n equals a,t,g, or c

<400> 67
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tatgatcaat ctctacagtc ccctgatgaa tttcacaggt tcccaccacc atcagttcta 180
cctattcatc tcatccatgc tcattgttct gcctctttcc tgttcctatg gatgccctgg 240
catgtttgtt tctttctttc tggcctccta tttccctccc ctcagacatc acttcagcat 300
ctgtgccttc tcacttccct tatcctgggt gttaccattt cagcctatga gcatgccatt 360
aatttgccat ctttacaaaa ttctctcttg acttcacatc cctctgtagc tgccctctcc 420
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tcactcctat aatcccagca ctttcagaag ccaaggtggg aacatcactt gaggccaaga 540
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actcganggg ggggccggta nccaattggc ctaaagtgag tc 642

<210> 68
<211> 802
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (105)..(105)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (730)..(730)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (755)..(755)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (757)..(757)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (777)..(777)
<223> n equals a,t,g, or c

<400> 68
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tttttcctaa agaataacwt gaycctttgc caracggact acgaggaagg tttaatgaaa 180
gaaggttatg caccccmggt tcgctgatct atcaacatca ccccattaag aatacaaagc 240
actacattct tttatctttt ttgctccaca tgtacataag aattgacaca ggaacctact 300
gaatagcgta gatataggaa ggcaggatgg ttatatggaa taaaaggcgg actgcatctg 360
tatgtagtga aattgcccca gttcagagtt gaatgtttat tattaaagaa aaaagtaatg 420
tacatatggc tggatttttt tgcttgctat tcgtttttgt gtcacttggc atgagatgtt 480
tattttggac tattgtatat aatgtattgt aatatttgaa gcacaaatgt aatacagttt 540
tattgtgtta ccatttgtgt tccatttgct yctttgtatt gttgcattta gtacaatcag 600
tgtttaaact tactgtatat ttatgctttc tgtatttacc agctatttta aatgagctgt 660
aactttctag taaagaattg aaaagcaaat cctcactaaa ggatacacag gataggataa 720
agccaagtcn catcaacatt aaaaaatact aaaananaaa acacaaaaaa aaaaaanccc 780
ggggggggcc cggaacccat tc 802

<210> 69
<211> 470
<212> DNA
<213> Homo sapiens

<400> 69
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taataagagt tccacaatca atagaaatct atcttggcag gcacttcctt ttacccacta 180
gaatttttc ccttgggagt tcacgatccc cagaaactgt gatatgagcc attcaatatt 240
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aaatcttaca gacttatatg aaagctgttg ttaacagctg ggtactagtt atttgaaaag 420
tttctcgtgc cgaattcgat atcaagctta tcgataccgt cgacctcgta 470

<210> 70
<211> 1881
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (70)..(70)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (126)..(126)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1860)..(1860)
<223> n equals a,t,g, or c

<400> 70
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acagcnctgc tagtagagcg aagtatttat taatacagaa ttaaccttmg ccccttttaaa 180
gtcaagtctg tctaatctaa ctagcgcctc gctttgcctt ctcacaatgc tcactagcca 240
tcatgctcac ccttctcttc cagatccact tcctcatgat actgtcttct aactgggctt 300
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aatattggag gtttcatgtt agccatttta aaaggcaaca ctttgacaaa atgatcgttc 660
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caatggaata tgtcacactc cttaataggg acctgtgact ccttaataag gacctgtgac 780
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ctgcggccga caagggaatt c 1881

<210> 71
<211> 541
<212> DNA
<213> Homo sapiens

<400> 71
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agcagagctg gaccagcctg gccaacatgg tgaaacccca tctctactaa aaatacaaaa 480
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c 541

<210> 72
<211> 762
<212> DNA
<213> Homo sapiens

<400> 72
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tggcaggaat gcctacataa cagggaaaaa tctattgatg caagcacggt ggttccatat 180
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gcggcaatct caggaaaaat aaagcaggag tggtcattca ctgtaaccac aggatcccat 300
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aataaatact aatggcagaa aaaaaaaaaa aaaaaaaaaa aa 762

<210> 73
<211> 1103
<212> DNA
<213> Homo sapiens

<400> 73
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ctgatcatcc cattgtactg caaaaaccag aaaacaacca aagttttaag tagcatttta 180
agaacagatg aatttaagtt tggacatctg caaatgaggt ggatctagca acaataactg 240
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gctgctactt atgtcactaa tcagaccata tgaatagcag aagttgagca atttcaaagt 900
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tcctagaaat tttatacatt aaatctcctg caatttgtca ctctggatgt tactgtttaa 1080
aaaaaaaaaa aaaaaactcg tag 1103

<210> 74
<211> 1633
<212> DNA
<213> Homo sapiens

<400> 74
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<210> 75
<211> 1384
<212> DNA
<213> Homo sapiens

<400> 75
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<210> 76
<211> 1715
<212> DNA
<213> Homo sapiens

<400> 76
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<210> 77
<211> 1437
<212> DNA
<213> Homo sapiens

<400> 77

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ggcccccttcg ggcccgcggc tgcgcttccg acggggcggc cgggggctca gagatccaag   180
tgcgcgccct ggcgggtccg gaccaaggga tcactgagat tctgatgaac agaccttctg    240
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gggaggaccg gcaagtgcgt gtcctgctct tcagaagtgg agtgaagggc gtgttctgtg    360
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<210> 78
<211> 776
<212> DNA
<213> Homo sapiens

<400> 78

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aaaatatatg tactcttcac ttttgttcca gtactataat tgctcatgca ctctttctcc    120
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cctttgagaa cattcagtga aatacaactt catcaaagat ttgctcaaag gagaagaatc 180
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ataaggcagt tgacttctta agtaaaagca atagtgtaaa atgtcatttt gtttggaatg 720
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<210> 79
<211> 1155
<212> DNA
<213> Homo sapiens

<400> 79
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aaaaaaaaaa aaaaa 1155

<210> 80
<211> 407
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
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<223> n equals a,t,g, or c

<220>
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<222> (378)..(378)
<223> n equals a,t,g, or c

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<210> 81
<211> 711
<212> DNA
<213> Homo sapiens

<400> 81
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<210> 82
<211> 2152
<212> DNA
<213> Homo sapiens

<400> 82
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<210> 83
<211> 1555
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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<222> (1396)..(1396)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1551)..(1551)
<223> n equals a,t,g, or c

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<210> 84
<211> 1532
<212> DNA
<213> Homo sapiens

<220>
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<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1433)..(1433)
<223> n equals a,t,g, or c

<220>
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<222> (1446)..(1446)

<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1505)..(1505)
<223> n equals a,t,g, or c

<400> 84

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<210> 85
<211> 1559
<212> DNA
<213> Homo sapiens

<220>
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<222> (1445)..(1445)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1551)..(1551)
<223> n equals a,t,g, or c

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<210> 86
<211> 1231
<212> DNA
<213> Homo sapiens

<400> 86
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<210> 87
<211> 1189
<212> DNA
<213> Homo sapiens

<400> 87

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<210> 88
<211> 496
<212> DNA
<213> Homo sapiens

<400> 88

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agttccagga caccaaggtc tactgcactc gggaatctaa cccacactgt ggctctgatg     180
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gcttttgcag ccttcttttc tcacttctgc ttatactttt gctggtggat tcctttaatt     360
cataaagaca tacctactct gcctgggtct tgaggagttc aatgtatgtc tatttctctt     420
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<210> 89
<211> 3153
<212> DNA
<213> Homo sapiens

<220>
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<222> (1)..(1)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2584)..(2584)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2590)..(2590)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (3153)..(3153)
<223> n equals a,t,g, or c

<400> 89
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<210> 90
<211> 2496
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2340)..(2340)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2373)..(2373)
<223> n equals a,t,g, or c

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<210> 91
<211> 1001
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (919)..(919)
<223> n equals a,t,g, or c

<400> 91

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<210> 92
<211> 1142
<212> DNA
<213> Homo sapiens

<400> 92

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caaggaggac ttcgttttgc tcatcttctg gatcaggtct ccagagtaga tcctgaaatg    180
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gagacggagg aagatcacgt ccagacagtc tctttgctcc gggaagttca gtacaacatg    480
ggcttcctct ttgcctacag catgagacag aagacacggg catatcatag gctgaaggat    540
gatgtcccgg aagaggtaaa attaaggcgt ttggaggaac tcatcactat cttccgagaa    600
gaagcaacaa aagccaatca gacctctgtg ggctgtaccc agttggtgct agtggaaggg    660
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ct 1142

<210> 93
<211> 2238
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (12)..(12)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (45)..(45)
<223> n equals a,t,g, or c

<400> 93
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<211> 1052
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<211> 954
<212> DNA

<213> Homo sapiens

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<211> 1794
<212> DNA
<213> Homo sapiens

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<221> misc_feature
<222> (1675)..(1675)
<223> n equals a,t,g, or c

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<211> 1262
<212> DNA
<213> Homo sapiens

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<211> 2572
<212> DNA
<213> Homo sapiens

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<221> misc_feature
<222> (2527)..(2527)
<223> n equals a,t,g, or c

<400> 99
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<211> 1488
<212> DNA
<213> Homo sapiens

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<210> 101
<211> 704
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (287)..(287)
<223> n equals a,t,g, or c

<400> 101
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<210> 102
<211> 1022
<212> DNA
<213> Homo sapiens

<400> 102
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cg 1022

<210> 103
<211> 1766
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (14)..(14)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (36)..(36)
<223> n equals a,t,g, or c

<220>
<221> misc_feature

<222> (1750)..(1750)
<223> n equals a,t,g, or c

<400> 103
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cccgaattcc ttcttggacc aggaaagccg gagacgaaga ttcaccattg cagactcgga 180
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ggggccccan attacgcgtg agcgtt 1766

<210> 104
<211> 2286
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2262)..(2262)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2264)..(2264)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2272)..(2272)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2278)..(2279)
<223> n equals a,t,g, or c

<400> 104

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cgacgtagct tttggctttt ttctgggcta catgcagtac agcatcgtgg actattgctg    180
gctctcaccc cataatgctc cggtcctctt tttactgtgg agtcaacgat gacaccatct    240
cattgattat ggcaccagga agtctgaagg tttccacatt cgatgatgtc aacctaaacc    300
agcagccatc ccgcttgtcc ctcttaggca tttcaggctt cctttgggat ttcaggtgtc    360
ccatgatctt gatgtgctgc taggctggag cacacactgg ccattactga acacagccat    420
attagggaaa gcaaaaaaac ccaaaaaatc ctctattgta tatttattca acaactgttt    480
atgtttccag gacaactgca aagaaaacaa gctgaggtgg ttatactgtt gctgttaaaa    540
gttggtatca gtaagatttg tgttttgtga taatccctaa atcaacatac cacttgtaaa    600
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taggtttttc tagtttattc cctgaagatc tgttgccaca gttgggagat ttcttcttaa    780
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cagtgtccac aaatctgaat attaggggca tgaaattagg cttaccatct gatttgtaat   2040
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tagatcattt cacctgatgt tttgaagca tcctaagtac agtagagtag aaaactgatt    2160
tctttgttaa ttgtacactg aataatgcct tttaaaaatc aaaataaaat taacaaataa   2220
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tagtga                                                              2286
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<210> 105
<211> 1240
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1225)..(1225)
<223> n equals a,t,g, or c

<400> 105

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gaactggagc taaggctaag tggtctgtct gtttaataag agtttgaatc agatggcctg    180
gcatgaagag tcactggcct gagagaatgt caggggcatt tgtaaatgtg taaagggctg    240
aaaaatcctg agggattatt attattgcta ttgttgttat tattcacaga cacatccaac    300
agccattgtc tgcctcctta tctgtcatgc tttctgcacg agcgtcagcc tgagcttcaa    360
tctgtgtgta tatctgcagc ttacgtcctt gccacccctc cagaacccag tttcatcctt    420
gtaggttttt ccgaagcagg atttgcacaa gtggcgtgtt ttcttaagta tttattttgc    480
aggccattta ctcggcatgg ctatttttac agtgggtaag gagcaaggct aaaaataact    540
tagctcataa ccagacaggt tctgcatttg acatttacgt ggaattcatt tgcatctcat    600
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ttgttcgcct ttctgtttaa caggtagaat gtaagaaagc tcagccgaaa gaagtcatgt 660
tcccacctgg gacaagaggc cgggcccggg gactgcctta caccatggac gcgttcatgc 720
ttggcatggg gatgctgggt gagtctggac aggaccgcag gtcaccatgg actgggaggg 780
ctatggaggc ctctactccc aactgggtca cctaccagtg ggcaaactg cttcaccttt 840
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ttttctaaaa ctkgggagag gagggaagtg gtaagggtgg gcgataatcc tgtctattta 1200
aatgattaac atttttctct tgggntatca aaatttgcat 1240

<210> 106
<211> 997
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (963)..(963)
<223> n equals a,t,g, or c

<400> 106
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cgcccccgagg cggtagcttc agagcctcca gtgcctgtgg ggctggaggt gaagttgggg 180
gccctggtgc tgctgctggt gctcaccctc ctctgcagcc tggtgcccat ctgtgtgctg 240
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ctntttcatc ccaaatttaa gggggtttca agaagaa 997

<210> 107
<211> 312
<212> DNA
<213> Homo sapiens

<400> 107
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ggtgcatttt gtgtgtgcct tccagagcca gtggactggt gtgtatccaa tgatgccacc 180
tctgaaacct acagaaccac tatgctttgc atgtgtaccc tgcagggtct gagggccagg 240
ctgtctggta gctctgctcc tgggtgacag agcaagactc tgtctcaaaa aaaaaaaaaa 300
agggcggccg ct 312

<210> 108
<211> 864
<212> DNA
<213> Homo sapiens

<400> 108
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aaaaaaaaa aaaaaaaaa aaaa 864

<210> 109
<211> 1258
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1196)..(1196)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1200)..(1200)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1237)..(1237)
<223> n equals a,t,g, or c

<400> 109
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cacaagtaca tcccccggag ggcagtgctt tatgtacctg gaaatgatga aaagaaaata 180
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aggaatttaa ccggatggga agtttttaa acttttncaa ccaacttttt taaggccc 1258

<210> 110
<211> 883
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (19)..(19)
<223> n equals a,t,g, or c

<400> 110
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<210> 111
<211> 1465
<212> DNA
<213> Homo sapiens

<400> 111
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ttaaaaaaaa aaaaaaaaac tcgta 1465

<210> 112
<211> 1369
<212> DNA
<213> Homo sapiens

<400> 112
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<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

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<220>
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<223> n equals a,t,g, or c

<400> 113

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<211> 629
<212> DNA
<213> Homo sapiens

<400> 114

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<210> 115
<211> 2497
<212> DNA
<213> Homo sapiens

<400> 115

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<211> 1217
<212> DNA
<213> Homo sapiens

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<210> 117
<211> 529
<212> DNA
<213> Homo sapiens

<400> 117
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<210> 118
<211> 1146
<212> DNA
<213> Homo sapiens

<400> 118
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aaattc 1146

<210> 119
<211> 1346
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> misc_feature
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<223> n equals a,t,g, or c

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<221> misc_feature
<222> (1115)..(1115)
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<211> 1079
<212> DNA
<213> Homo sapiens

<400> 120
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<210> 121
<211> 2103
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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<211> 1212
<212> DNA
<213> Homo sapiens

<400> 122
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tggtcgtgcg agtgctgtgg tggattggca ttctgacgtt gtatctcatg cacagaggaa 240
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aagacgacca tactcgggtt gcttyttcga gtacggcaga gcttttctca acctactttt 780
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<210> 123
<211> 616
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (17)..(17)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (580)..(580)
<223> n equals a,t,g, or c

<400> 123
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tgtggctgtg gtggtgtggg tctttgcctg tggacccgtg gaagacaaag aagacagttt 180
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aaccaggact gtgagggcag gaaggcttgg ggtctttgtg tgctgagcct cattagggtt 300
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tcactgttga ttattgccct caagaataac aggttgccca gctactcgag argcttaagt 480
gggaggattg cttgacccca ggagttcgag gctgcagtga gctatgatcg cttcactgcg 540
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aaaaaaaaaa ctcgag 616

<210> 124
<211> 536
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (536)..(536)
<223> n equals a,t,g, or c

<400> 124
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ccttctcttc tttccttctc tgtcacacca ttcttctgtt ccttggctct tctgctcatc 180
tccttgtgga gscawaggtt tggggtttat atgagtacag gataggtgac atggtggatc 240
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ccagggttga gggtggggcc tttgctaggg aaccaccctc ttctacccag tattttcctg 360
tctcctgtct gtatcaatag gtacacaata twtattaaat taatkaatga ctatacatta 420
tgaaatggga aatgcaaggt ataaaggaga attgctgtcc ttgaaaagaa atttagtttg 480
tttttttgtt gagatggagt cttgctctaa gctagagtgc agaatgtaat caaggn 536

<210> 125
<211> 796
<212> DNA
<213> Homo sapiens

<400> 125
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gaccargtag agtgatgggt tgtacagcac tgttactcct tttccatctc tgtgtcccat 180
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gatgagaaaa caggatcaga gtggtacaga tattggtcta agtcacagag aaagtgaatt 300
gtaaaagcag aaacagagca caggctgcct gacttctagt ccagtgcttt ttgctcaaat 360
tgcctcttat ttctcaggtt attcttgaaa tggcagatgg ggattctgtt taatgaaaca 420
aaagtgacaa ttctttcttt cttggagaga aggtggagac agggtctcac tctatcacac 480
aggctggagt gcagtggctc aatcatggct cactgcagcc tcaatctcct gggctcaagt 540
gattcttcca ccttagcctc cttgactcac tgggactaca ggtgcacacc accatacctg 600
gctaattttt aaagtttttt gtagagacag ggtctcacta tattgtgcat tctggtcttg 660
aactcctggt cccaagtgat cttcctgcct cggctttcca aagtgctgga attacaggca 720
tcaccccccat gcctagcctg aaaattcttt ctatgtcctt aacatcttct ttcccagtat 780
ttctccatcc actcga 796

<210> 126
<211> 1037
<212> DNA
<213> Homo sapiens

<400> 126
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ttccaccttc ttgtggctgc tggcattctt tggcttgtgg tcacatcact cctatcttga 180
aggccagcat cttcaaatct gtttcttctt cacatagcct tctgtgtgtg cagtgccctc 240
tacctctctc ttataaagac atttgtgatt aaatggaggg tttaggataa tctcgtcaag 300
atccttaact taatcacaac tgcaaaaacc tctttcccaa ataaggtaac attcacaggt 360
tccagggatt aggacctatt atctttggta agtattattc agcctaccac aatagctaaa 420
acaattctga aaaagaagaa taaagtgaga gaaatcagtt tatctgattt cgatacttat 480
tgtatagcta tggtaaataa ggctgcatgg tattaaagaa aggacatata tgaatgaaac 540
agaatagagg acccagaaat agacccacac aaaggagccc aaattatttt taaccaaggt 600
agaagacaat ttattggagg aaagacagcc ttttcaacaa atggtactat aacaattaga 660
tatccatagg caaaaaaaaa aaaaagaatc ttgatctaag gctcacacct tatataaaat 720
aatattaaac tcatggccag gcacagtgac tcatgcctat aatcccaata cactgggagg 780
ctgaggcaag agtatcactt gaggccaggg gttcaagact agcctgggca acacagtgaa 840
actctatctc tacaaaaaaa ttataaacta gctgggcatg gtggcacatg cctgtagtca 900
caactactca cgaggctgag aagatcactt aagctgagtt gttcaaggtt ctaatgagct 960
acaatcgtgc cactgcactc cagcctaggt gacagacaaa gaccccatct caaaaaaaaa 1020
aaaaaaaaaa actcgta 1037

<210> 127
<211> 841
<212> DNA
<213> Homo sapiens

<400> 127
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aatgtttaca ctccatgcac aatctgtgct tccagtccct caccctatgt ggcccaatag 120
ctggctggat ttcacactta attggtattt ttttctgcct tcttcccctg cccccactga 180
ctcctctcct ctccctttga ttgtactcaa ggttctgggg cctgggccct gggtgggtac 240
caacagctgc tcgctgttcc catgtcctct ctccagcttt gctgtgtttc tctgctacct 300
aatctcagtg actgtgaaag gacattgtgt ctgagccatg gccagccgct ggctggcccc 360
ctgatctgcc ccccttctat tgtttggatg gccatctcct gctgggcctc cctgactgta 420
aaatctctgt actgtttgtt aggtttttgg tgggaggctg tgataagttc caatgagctg 480
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gcccccagtt cagccccagt caccctcttt tacacatgtg ggtcaaccac tgtgtgctca 600
gagggtcagt cccttcctct gctgtgtttt tcttgagtcc ttgcactcac ttcccctgcc 660
ccagtcacga tgacccctaa agcttccttt gcccttgctt tctagggcat ccctagtgaa 720
ggggcaaacc tgagatttct ccgtggacct gacagccaag gcagggcact gtctcctgag 780
gccagtgcca gcacgtgcat ggttcacaga aaaggatcct gggctcagaa tctcgagggg 840
g 841

<210> 128
<211> 2128
<212> DNA
<213> Homo sapiens

<400> 128
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ttctccctgc tttccccaag ccacccgcct tgaatctggg gtgctctacc agacccatcc 180
cctcatttct aaagatttga gccactagtc gtgtccctct ccctcagaaa tgccttggtg 240
acacttggct gctttcaact cttccaccca tctgcctctt ggtctcatct ttaccttctg 300
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acctgtcccc gacccctggg accactgacc gggcccgatc accctgtcac tgccctgtca 480

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ggaaggcttt tcctctgtga gccccaggcc accctttccc tcctttaagt aattacttaa     660
gtcccttgcc agggccctcc cagtaccctt tctaaagaca cccctgcccc agcatgctgc     720
aggctcctgc tccactttcc tctcaggccc tcgtcgctgt ggtgctgcct ttgttttctg     780
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ctgccccacc tggacacatg gctcgagg                                       2128
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<210> 129
<211> 748
<212> DNA
<213> Homo sapiens

<400> 129

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ttttagccat cctaataagt gttagtggct atcattgttt tcatttgcaa ttctcttaca     180
tggtgtkgaa catctttccc catgtttatt tgtcatctgc atatcttctt cggccagtta     240
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aaagaaagct ttttttatta ttgagttgta atagtgcttg tatagtgtgg ataacagttc     360
tctatcagat aggtcttttg caaatatttt ccccaatctg tggactgtct tctcattctt     420
ttgataaatg gctttaaaat aataatctgg ccgggcgcag tggctcatgc ctgtaattcc     480
agcactttgg gaggccaagg gcagatcatc tgaggtcggg agttcgagac cagcctgacc     540
aacatggaga aaccccatct ctactaaaaa tataaaatta gtcgggcgtg gaggcacatg     600
cctgtaatcc cagctacttg agaggctgag acaggagaat ctcttgaacc cgggaggtgg     660
aggttgcagt gagccgaaat cgtgccactg tattccagcc tggacaataa gagcaaaact     720
ccatctcaaa aaaaaaaaaa aactcgag                                        748
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<210> 130
<211> 297
<212> DNA
<213> Homo sapiens

<400> 130

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tatttctttg aatgagaaat tggctcccat gattatggag ctgacaactc ccaaggtctg     180
caggcagcaa gctggaggcc caggagggcc ggtggtgtgg ctgcagccag tgtctgaagg     240
cctgagaacc aggagggcgg gtggtgcagc tgcagtgtga aagccggcag gctcgga        297
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<210> 131
<211> 1894
<212> DNA
<213> Homo sapiens

<400> 131
ggcacgagca gtctacctgg aaattgtcac attatacaaa tgtcaacttt tgtgtgtgtg 60
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aataccaaga ggtgtttact gactaaaggg caaagggatc tatcagttaa ccaaagcaag 180
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<210> 132
<211> 1355
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1327)..(1327)
<223> n equals a,t,g, or c

<400> 132
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catttccctt ctgtgtcctc tttcgtgatc ttgaggtggg acttgggttt gaaggctttg 180
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ttctgaactt tcttgctctt tcagaattgc gttttgaccc tgagtgtggt cgtgggtgac 1260
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<210> 133
<211> 1382
<212> DNA
<213> Homo sapiens

<400> 133
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atgaacgacc ctaccaggac ttttgccaat ggcagcctgg ccttcagggt ccaggccttt 360
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tgggacttgc aggcctaaat gagaggcatt ctgactggtt ggctgccctg gaaggcaaga 1320
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aa 1382

<210> 134
<211> 791
<212> DNA
<213> Homo sapiens

<400> 134
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agcggagtga cagcaacccc agagatgagg caccagagag tgccactgca tgagacacct 660

gtgaccattc gaagtctgaa atgcgggggg ggagtttcat ttttaagtga agaccaaaag 720
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agggcggccg c 791

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<211> 2163
<212> DNA
<213> Homo sapiens

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<210> 136
<211> 2087
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

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<210> 137
<211> 830
<212> DNA
<213> Homo sapiens

<400> 137
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<210> 138
<211> 1939
<212> DNA
<213> Homo sapiens

<400> 138

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aatttttcag tttctgtgag aattttataa tttataattt gcagacttaa tgtataatct    180
attttgtcct aacaattaca aatatatttt ttatttcaga ttrtatatat tcctaccaga    240
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aaatttttat ggacacataa taactgtaca tatatatggg gtagaatgtg atgttttaat    360
acatgtactc aatgtgtaat gatcaaatca gggtaatttg cataatgatt tttctgtagg    420
gagaaaattc aaaatctact cttctggcta ttttcaaata tataatatgt tattgttaac    480
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aaaaaaaaaa aaaactcga                                                1939
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&lt;210&gt; 139
&lt;211&gt; 2410
&lt;212&gt; DNA
&lt;213&gt; Homo sapiens

&lt;400&gt; 139
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<211> 1491
<212> DNA
<213> Homo sapiens

<400> 140

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<210> 141
<211> 3530
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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<221> misc_feature
<222> (59)..(59)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
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<223> n equals a,t,g, or c

<220>
<221> misc_feature
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<223> n equals a,t,g, or c

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<221> misc_feature
<222> (3487)..(3487)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (3505)..(3505)
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<210> 142
<211> 1145
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (386)..(386)
<223> n equals a,t,g, or c

<400> 142
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tattgaaccc agaaatcatt gtctagcaaa agccagtata gtgattaatt accctgtgac 780

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raactactca tccagaattt tgtcraaaaa gaaaaataag ataaaattca ctggtagaca    960
aaaagtagta acataccagt ttgtaatttc tcagtttcaa accatgaata tgtatttgta   1020
taccaaaaat catttcagga gtcagagaag gaggatatgc cttttatgtg gagactttaa   1080
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cctgt                                                               1145
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<210> 143
<211> 2214
<212> DNA
<213> Homo sapiens

<400> 143

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cagcaagggg gattcagtgc caatgcatca acaaaaaaga caaccagagt tagtggaagg    180
aaatcttcct gttttcgtgt tccccacgga gctcatattt tatgcagatg atcagtcaac    240
acataagcaa gtgttgacac tgtacaatcc ctatgagttt gccttaaagt tcaaagtttt    300
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ttgtgtggat attgtgattc gtcatcgaga tgttcgatcc tgtcactatg gtgtaataga    420
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taaaggraca tttaackgaa aktttatttt ttgagcagtc gtttcaacca ggtcttatca    600
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aatcttgtga attacagaac aggttgtggt ccagacacca agaatcatag ggggtttttt   1260
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<210> 144
<211> 813
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (283)..(283)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (691)..(691)
<223> n equals a,t,g, or c

<400> 144
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gtttaatttg tagcatttgc cagtttctgt ggtgtaaata ctcccactac agctgttttc 120
aagctaacat tgtgatacca caaaaaatgg aattgggaag gcacaatcaa gattaacaag 180
ccagtttaga ccaagacaat ttttctgccc tattagttgg gcacaagtta gaaaggctga 240
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attgaagtgc cctgtttgag ggcatgctgt tagtaacttt taaaatatga gatgtcatac 360
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aatatacaaa aataactgtc attgcagcat tatttgtaat agtggaaaca gaagactttt 480
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<210> 145
<211> 1739
<212> DNA
<213> Homo sapiens

<400> 145
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<210> 146
<211> 1677
<212> DNA

<213> Homo sapiens

<220>
<221> misc_feature
<222> (1012)..(1012)
<223> n equals a,t,g, or c

<400> 146
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<210> 147
<211> 2648
<212> DNA
<213> Homo sapiens

<400> 147
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<210> 148
<211> 1084
<212> DNA
<213> Homo sapiens

<400> 148
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tgtcttagtg tgactgtgat tctttctctc cttttgtctt tcagcaaacg gggattcagc 180
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<212> DNA
<213> Homo sapiens

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<211> 1251
<212> DNA
<213> Homo sapiens

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<211> 1539
<212> DNA
<213> Homo sapiens

<400> 151
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<212> DNA
<213> Homo sapiens

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<211> 2108
<212> DNA
<213> Homo sapiens

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<210> 154
<211> 1146

<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (857)..(857)
<223> n equals a,t,g, or c

<400> 154
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<210> 155
<211> 1998
<212> DNA
<213> Homo sapiens

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ttaaaaaaaa aaaaaaa 1998

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<211> 970
<212> DNA
<213> Homo sapiens

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accacaggac taactgactg aaccacactc caccatttgc ccctatttcc aggcgttatg 180
gtcaccctgt agtttctaat ctgtatagat gtgtagagca tgcctcttcc ctcttccttt 240
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tcttgcattt tctttcaact tgggccaaaa aaacaggcaa cattttcttc ctccactacc 420
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gtctattatt aagtctaaca acttagcttc gaacctcaat ccaagcatct gacaacacac 540
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cactttggga ggccaaggtg ggatcacctg aggtcgggag ttcgggacca gcctggccag 660
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tgtcatccca gcaaggcagg cgaatcgctt gaacccggga ggcggaggtt gcggtgagcc 780
gggatcgtgc cattgcactc cagcctggtc aacagagcga gactccgcct cattaaaaaa 840
aaaaaaaaaa aaaactcgta g 861

<210> 165
<211> 587
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (587)..(587)
<223> n equals a,t,g, or c

<400> 165
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aaagattgtt tctttttcaa tgcaagttca cagatcactg gagttctagc tacagtttgt 180
tctagaccag aggttgcaga tatttttgtc ctataaagag acacatggtt aatatttttg 240
gctttgtgag ttgtatagtt ttccgttgta gctgttcagc tctgctacat gaaagcaacc 300
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ccaagactgg ctccctacct tggctgacaa attctcactt tgggacttag tcattgttgc 480
tgctctctgt tattttgcat gtcttttctc atgtttaggt gctgtgtctt aatacttttt 540
tcttacattt aatttaacaa tcattactga gcgctggtat gtctagn 587

<210> 166
<211> 477
<212> DNA
<213> Homo sapiens

<400> 166
gaattcggca cgaggtgagt atggcttttg tcttccatct tgctcagggt actttggaac 60
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ctagtacttc aacatggaga caattatctt ttgtttttgt tttgttttgt ttgttttgtc 180
ttggccatgc ctttttgagt ttaccttttt atatttgtc catcattgcc atgtgtttgg 240
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ctgtgcactt tcttgatgat tcgggcttat ctttatgact gtctgtkttt gtgtcagact 420
gtaaagaagt ataaaagtct ttagcttgaa aaaaaaaaaa aaaaaaaaaa aactcga 477

<210> 167

<211> 1930
<212> DNA
<213> Homo sapiens

<400> 167
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tcagggatga tgtctaatat tactcaatca cattcaagta aaatatcagc ctttggtatc 180
ttcattggac cagaacagtt tctttagatc ttcttatttc tctttcaagc ttcaacctta 240
aataataggc cattgtgtag cagaaaaaac tttaaactta gaagtagaaa tctataatca 300
aatcctcagc caacttaaaa acagttgtgt gaccttggat aagtcccata gccggactgc 360
attctctaaa ccagcagcta taacgtttcc tacctcatta gagtgtggtg tgaatgaaaa 420
tgtgaagaat gcctaaaaca gagtcaggcc ttgaatgcat tagaaagttt caggcagcca 480
ctcattccat caccctgtct cactctttct agtgacccag ggtcacttac ctgtttttct 540
taatacaccc caagtctttc tcttgcctct ctttgtagac cagaattatt cttgtgttca 600
tcaatatgga ttgagtcaaa aattttcaag atctacctga cttattactt caaggatcca 660
tcatcctctg gcttccattt ttttgtattt ctataggcat ggattcaaag gggatatctg 720
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aaggaagagg aagttaatct gagacaggat tgtgacaggc agaccaataa acatgtctgt 900
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caaagacaga ggcacaggga gaagacagat ctatccaagg tcactcaagt gaggaaataa 1260
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tgcctataca gcaacattaa tgccagcaag gaaggaacct gagggttaaa tccttggccc 1380
cagccccaga tagcaataca gaaccccacc cccgtaattc agtcaataaa tagatgtccc 1440
tttcatacaa gtttcagaaa acacagttaa tatacaacca ctactcacaa attaaataag 1500
ttatcttact gtaaaggata taactatttt attatctttg caattaaaat gaaatatgct 1560
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tttataaaat agagcaaagg gagcccagtg ctttgagaat gccaatgcaa aattataata 1860
attacttatt acatgataca gttgttaaag tattttctgt gttgttcaaa aaaaaaaaaa 1920
aaaaactcga 1930

<210> 168
<211> 1021
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (248)..(248)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1004)..(1004)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1014)..(1014)
<223> n equals a,t,g, or c

<400> 168
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acggttcgtt ttggttctat gtactctcta aaatgttatc gtttttcatt tgtctactaa 180
ttttcgtgca tttgttacta ctgagtttct taatatctga ctggcctccg cccacgggct 240
ctgcaganca taaaatactc aggctgatgg tagtgcagag actctccctc cttgatcagc 300
gcaaacgttg gtctgaggct tgagggatgg agcaacattt tcttggctgt gtgaagcggg 360
cttgggattc cgcagaggtg gcgccagagc cccagcctcc acctattgtg agttcagaag 420
atcgtgggcc gtggcctctt cctttgtatc cagtactagg agagtactca ctggacagct 480
gtgatttggg actgctttcc agcccttgct ggcggctgcc cggagtctac tggcaaaacg 540
gactctctcc tggagtccag agcaccttgg aaccaagtac agcgaagccc actgagttca 600
gttggccggg gacacagaag cagcaagarg cacccgtaga akargtgggg caggcagarg 660
aacccgacag actcaggctc crgcagcttc cctggagcag tcctctccat ccytgggaca 720
gacagcagga caccgaggtc tgtgacagcg ggtgcctttt ggaacgccgc catcctcctg 780
ccctccagcc gtggcgccac ctcccgggtt tctcagactg cctggagtgg attcttcgcg 840
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agccttagat agcagcagaa ggctttttgg attctcctcc ttgaaaagat tctcagttac 960
caaacgtctc cacctagaaa ataaaaatac attaagatgt tganaaaaaa aaanaaaaaa 1020
a 1021

<210> 169
<211> 727
<212> DNA
<213> Homo sapiens

<400> 169
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aggtgttgac cagcaatttc ctgcggcatt tacttcttga taacaagagt gagaagatag 120
agacagggca gatagacact taagagtaaa atgtattaac acaaaggctc tggccgcccc 180
cctacaaagg aggccatgga accgatggaa ctgatggagg aaatgctggg actgtgggtc 240
agtgctgaca cacccatggc catacgtttg gtcttcttgg ccttggctgg gctggtggat 300
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ggaagtacct ggggaagcag gagagactca cactgctgtc atggccccac agcctggagc 420
ctcccctgcc tcctctgcct cttcagagcc cagcagaaag acagagaaag aagcctcctt 480
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gtagaaggca aggatgattg ggagtagaag gaagagtgac aggctagcat gagctgtgca 600
gcagcaagat tccatatgag caaagttcag aaagtgrgmm aaaaggacca agttggatct 660
cctcctaacc ctgacctgca tgatatgggt gtgagaagct tcaactgaga aagctgctga 720
gaaagta 727

<210> 170
<211> 1341
<212> DNA
<213> Homo sapiens

<400> 170
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caaatagggt tgtgtgtgtg gctggtggtc ataaggtcct ttctggctct aataacctga 120
gcttctgtta tgaagctggg acccttagag cctcaggatg atcctctgtt tgtttgtgaa 180
gccccaatca ggtgctaagc accatagtgg cacttagctg aagctcctct gtaactcctg 240
tgggccctgc cttgcccacc cccgacagct gctgcagtgc tcctgagcag cacaggcctg 300
atggagcttc tggagaagat gctggccctc accttggcaa aggcagattc tcccaggact 360
gcactcctct gctctgcctg gctgctcact gcctccttct ctgcccagca gcacaagggc 420
agtttgcagg ttcaccagac actctctgtg gaaatggacc aagtattgaa ggctctcagc 480
tttccaaaga aaaaggctgc actactctca gctgccatct tatgcttcct gcggacagcc 540
ctgcgacaaa gcttttcctc tgccctggta gccctggtgc cctcaggggc ccagccactg 600
ccagccacca aggacactgt cctagctcca ctgcgaatgt cgcaagtccg gtccctggtc 660
attgggctgc agaacctcct ggtgcagaag gaccctctat tgtcccaggc ctgtgttggc 720
tgcctggagg ccttgcttga ctacctggat gcccggagcc cagacattgc tctccacgtg 780
gcctcccagc cttggaatcg gtttttgctg tttaccctct tggatgctgg agagaattcc 840
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gtcctctctc atgaagaggt gggtgatgtt ctgcaaggtg tggctttggc tgacctgtct 960
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cctagcacct cctcaggcca gccacccctg caggacatgc tctgcctggg aggggtggct   1140
gtatccctgt cccacatcag aaactgatcc tcaggacttg aaggcccaga agtggagaga   1200
gaatgagacc tggagacaaa gggcataatt gttggggaaa tggatgacag ctgaagctat   1260
tcatatggag ccatatactc tattgttgaa atagaataag gaaataaaat gatacactca   1320
cataaaaaaa aaaaaaaaaa a                                              1341

<210> 171
<211> 839
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

<400> 171
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aactgcctcc gctgctggcc agaactgtct gccttgatag actatgacct gcagatcctc    120
tgggtgaccc cagggccacc cacagaactt tctcaaagta ttcactcctt gttcctagag    180
gataataatt ttctcaaacc ctggtacctt gatcgtgacc atttggaaga agaaacagcc    240
aaattcttca ctcaagtaca ccaagccatt aaaacgttac gagatgataa aacagtactt    300
ctggaagaga tctacacgca caagaatctc tttactgaga ggctgaataa gatatctgat    360
gggctgaagg agaagggagc cccacccctc tccatgaatg ccttcccggc tccatctcct    420
acttgcaccc cagaacccct tggctctgtc tgcctcccca gcacctcagt ttctctacct    480
tctcaccctc cctggcagcc tgcaatgagt cctgtgccag gaaccggcgg acctccctgt    540
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gcaaaggaag aaggaggcag taaaggaaca gggcagcccg catgtcttcc agaagtgaac    660
agaggccgca gctaccaccg tcacaaagtt cactcatctc tgggtcccgg tgaccccatc    720
cccccatacc ctccatcctg ggtcctgggg ccccaaagct ctgaggccta ggagactgcg    780
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<210> 172
<211> 1022
<212> DNA
<213> Homo sapiens

<400> 172
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ggcgaggagg agccgccacc gcctcctcct gctgctgctg cgctacctgg tggtcgccct    120
gggctatcat aaggcctatg ggttttctgc cccaaaagac caacaagtag tcacagcagt    180
agwgtaccaa gaggctattt tagcctgcaa aaccccaaag aagactgttt sctccagatt    240
agagtggaag aaactgggtc ggagtgtctc ctttgtctac tatcaacaga ctcttcaagg    300
tgattttaaa aatcgagctg agatgataga tttcaatatc cggatcaaaa atgtgacaag    360
aagtgatgcg gggaaatatc gttgtgaagt tagtgcccca tctgagcaag gccaaaacct    420
ggaagaggat acagtcactc tggaagtatt agtggctcca gcagttccat catgtgaagt    480
accctcttct gctctgagtg gaactgtggt agagctacga tgtcaagaca aagaagggaa    540
tccagctcct gaatacacat ggtttaagga tggcatccgt ttgctagaaa atcccagact    600
tggctcccaa agcaccaaca gctcatacac aatgaataca aaaactggaa ctctgcaatt    660
taatactgtt tccaaactgg acactggaga atattcctgt gaagcccgca attctgttgg    720
atatcgcagg tgtcctggga aacgaatgca agtagatgat ctcaacataa gtggcatcat    780
agcagccgta gtagttgtgg ccttagtgat ttccgtttgt ggccttggtg tatgctatgc    840
tcagaggaaa ggctactttt caaaagaaac ctccttccag aagagtaatt cttcatctaa    900
agccacgaca atgagtgaaa atgatttcaa gcacacaaaa tcctttataa tttaaagact    960
ccactttaga gatacaccaa agccaccgtt gttacacaag ttattaaact attataaaac   1020
tc                                                                  1022

<210> 173
<211> 1028
<212> DNA
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<213> Homo sapiens

<400> 173
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acattcaaac ctggttttga tactggaaac tcttccttta aaactgtgac catgatttca 180
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tgcaggggtg aacctttgct cttctgtcag gcgaggccca ggctgcacca gccacctgcc 420
acatggtgac agtgccacgg gccctgcgta tggcccctgc aaccgtgctc tggcgggcac 480
acctggctgc tgcaggccaa ggccgctgtt cagtgaagag tcccatgttt agtatggact 540
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aaagtcatgc actttattta taggctctat gttttggctt ctgcagtact tttattatct 900
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agaaagatga tgacactaag ttgtgaaaat atgttgtgat ttttatgaaa taaactcacg 1020
gcacgtag 1028

<210> 174
<211> 808
<212> DNA
<213> Homo sapiens

<400> 174
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cccaacctag attcacatgg actgaaatgt gcatcttctc ctcatgggct ggttatggtt 180
ggagttgctg ggactgtcca tcgaggaaac acttgtttgg gcatttttga acaaattttt 240
ggactcatcc gctgcccttt tgtggagaat acttggaaaa tcaaatttat caacctgaaa 300
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caaagtgatc tagaggcctt ttataatgta atcactgtat gtggtaccaa tgaagtacga 420
cataatgtaa agcaggcttc ggatagtgga actggggacc aagtttgagg tagtggaaat 480
gagacattgc tgaacaaaag agaactgggt ttacctgacc ctctaaagcg ctaagtactg 540
tcagcctgaa aaaaatcttc tatacagaaa ctcttccaaa tactatatca gtaatgtctg 600
aatgatttca gatgtgaaaa ttgacatatt ttagttgaaa tacctttctg gactacagac 660
ttacatatca tgtgaatact tacctatttc tacccgagtt gcagcaagta ttctgaaagc 720
ttaatgcaaa taaatcccac tttagatctt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780
aaaaaaaaaa aaaaaaaaaa aaaaaaac 808

<210> 175
<211> 1898
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1398)..(1398)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1428)..(1428)
<223> n equals a,t,g, or c

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gtgctgagaa cctccatgtg aaaataagtt gctctctgga ctggttgatg gtctcagtta 120

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tcccagttgc agaaagcaga aatctgtata tatttgcgga tgaattacat ctgggaatgg    180
gctgccctgc aaatcggata catacatatg tatatgagtt tatatatctt gttcgtgatt    240
gtggcatcag gacaagggta gtttctgagg aaactctcct ttttcaaacc gagctgtact    300
ttaccccaag gaatatagat catgaccctc aggaaatcca tttggagtgt tccacctcta    360
ggaaatcagt gtggcttaca ccagtttcta ctgagaatga aataaaattg gatcctagtc    420
cttttattgc tgactttcag acaacagcag aagagttagg attattatct tctagtccaa    480
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ctaaatattt gtattcagta ggggtatggc tgattaattt aacattaact attaggtaat    720
tcatattata catttaagtt ctttctgttc tgtgtagaag attcagaaat atgtcttcaa    780
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gtaaaattta acatattaac tctcacgaaa ggcaaaatcc ttttatgtgc agatacttta    960
attcatgtag attttcctat taatcagtaa agttgaatcc taacaataat gccatgtgac   1020
aacctattta gattattcca gaattaaatt caatttattt tctagagctc aagtaaccac   1080
tactttaact gaaatttgat gttaggtttc ccttgttcct ccgaatggtt cttccacact   1140
caaaataatt gaatggttga gttggttaag caaagagtta tcctgccacc taagagcatt   1200
cattaaatga ttatttatta ccacctactt tatactatct tcctttcttt aaacatggag   1260
tctaaatatg taatatatca aaaaatactt ctgatttggt agatttctta tatcaagggt   1320
gagaattgaa ctgtgccatt ggctattcaa tagcttattg aatgtatgtt ttggatgcca   1380
catcctcctg gaagcaantt ttgccaagat actgtttatt attatttnta attaaagtga   1440
tactattcca ttttcaatta aatgctgtct gtagctgtta acttgtcaga taaagaattt   1500
gaccctgtca tagtgaacat ctgtctttac cagttaacat gcagctaaga ggtaatactt   1560
ctatgggact tcctaagggt cagaatatgg tacaagtaca ttgcgataaa ttatttaatc   1620
ttcttaaaga gtgaaatata tcatgattat cccaatttta cagataagca aacagaggtt   1680
aaatcatttg cctgagtcac ataacttgtt ggtgttggtt caagatttaa aatagggcaa   1740
tctgccttta gatctgtctc tatactctct ctttgtatat tagccactat actctactgc   1800
ttggaatcat cttaagttgc tgaactttag ttctctagaa aacaattgct attcaagcag   1860
ttatacaact ctcaataaaa cttaaagttg aaaaaaa                             1898
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<210> 176
<211> 818
<212> DNA
<213> Homo sapiens

<400> 176

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gcagttttga gagccctgtt tctgccttgt atcattttcc actgtgtatc kgattctagg    180
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<212> DNA
<213> Homo sapiens

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<222> (760)..(760)
<223> n equals a,t,g, or c

<400> 177

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gatggtagtg gaatatgctg agagtaccaa caactgccag gctgccaagc agtttggagt   360
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<211> 1481
<212> DNA
<213> Homo sapiens

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<210> 179
<211> 652
<212> DNA
<213> Homo sapiens

<400> 179
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taamatacaa aacttccccc agtcactggc cgccaggctg agttggggga tgtgttacat 180
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<210> 180
<211> 1711
<212> DNA
<213> Homo sapiens

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<210> 181
<211> 2058
<212> DNA
<213> Homo sapiens

<400> 181

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taaaaaaaaa aaaaaaa 2058

<210> 182
<211> 2398
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1874)..(1874)
<223> n equals a,t,g, or c

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<210> 183
<211> 1505
<212> DNA

<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<211> 813
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<211> 2288
<212> DNA
<213> Homo sapiens

<400> 191

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<210> 192
<211> 3758
<212> DNA
<213> Homo sapiens

<400> 192

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<213> Homo sapiens

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<223> n equals a,t,g, or c

<400> 193

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<210> 194
<211> 2664
<212> DNA
<213> Homo sapiens

<400> 194

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<211> 1076
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
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<211> 943
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<213> Homo sapiens

<400> 197
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aaaaaa 1566

<210> 198
<211> 1067
<212> DNA
<213> Homo sapiens

<400> 198
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<210> 199
<211> 2078
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1177)..(1177)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1187)..(1187)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2057)..(2057)
<223> n equals a,t,g, or c

<400> 199
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tcttgttgag tatcctgctg tggcccctgg tggtttatca tgagctgatc cagaggatgt 240
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<210> 200
<211> 2494
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (920)..(920)
<223> n equals a,t,g, or c

<400> 200
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<210> 201
<211> 845
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (4)..(5)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (823)..(823)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (845)..(845)
<223> n equals a,t,g, or c

<400> 201
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cggccgctct agaactagtg gatcccccgg gctgcaggaa ttcggcacga ggtcaaggca 120
aaaatgggtc aggtttggag agttccccca ctccttttga gtgttcaggt tttccttacc 180
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aagtcacaat ctatgggtgt agttctggga ttctgtcaaa ttctccttcc tgctctccaa 660
aatggacaat tgtcgtaggg accacatgcc cccagaatac aatggcctct gtgktctact 720
ggggtcaagc ctgctagaac tcagcattca tgacaggggs taagtgtgca tgaaktgaca 780
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tccan 845

<210> 202
<211> 738
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (3)..(3)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (8)..(8)

<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (566)..(566)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (680)..(680)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (684)..(684)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (703)..(703)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (715)..(715)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (717)..(717)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (731)..(731)
<223> n equals a,t,g, or c

<400> 202
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cgtttgctga gctgttcact gtttmtctct tctctttgga agcacctctc cgagccatgt 180
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ctggctcccc cacacctccc acctgcattg ctctccctcg tgctccccaa atcaccacaa 420
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ctgaaatggg ngaatggg 738

<210> 203
<211> 1145
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (9)..(9)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (410)..(410)
<223> n equals a,t,g, or c

<400> 203
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<210> 204
<211> 4909
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2488)..(2488)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2493)..(2493)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2512)..(2512)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2523)..(2523)
<223> n equals a,t,g, or c

<400> 204
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gcaagaagat ggtgtttctg cccctcaaat ggtcccttgc aaccatgtca tttctacttt 120
cctcactgtt ggctctctta actgtgtcca ctccttcatg gtgtcagagc actgaagcat 180
ctccaaaacg tagtgatggg acaccatttc cttggaataa aatacgactt cctgagtacg 240
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<213> Homo sapiens

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<210> 206
<211> 1259
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (4)..(4)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (18)..(18)
<223> n equals a,t,g, or c

<400> 206
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<210> 207
<211> 1314
<212> DNA
<213> Homo sapiens

<400> 207
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atcctgttct gcctccggct catgcacatt tttaccatca gtaagacgct ggggcccaag     240
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tgggtggtgt ccttcggggt ggccaagcag gccatcctca tccacaacga gcgccgggtg     360
gactggctgt tccgagggcc gtctaccact cctacctcac catcttcggg cagatcccgg     420
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cctcctctac cccaactgcc ctgtcacgcg cttccccgtg cccaacgaga aggtgccctg   1260
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<210> 208
<211> 468
<212> DNA
<213> Homo sapiens

<400> 208

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ttatttttgc aggtcctgac actaaactaa tgcagaatag tggtaagaca aagtttaaaa    120
ggacaagcat tgatagattg atgaatactc tagtactatg gatttttggg tttctgatat    180
gcttgggaat tattcttgca ataggaaatt caatctggga gagtcaaact ggggaccaat    240
tcagaacttt cctcttttgg aatgaaggag agaagagctc tgtgttctcc ggattcttaa    300
cattctggtc atatattatt attctcaata cagttgtacc catttcctta tatgtgagtg    360
tggaagtaat tcgtctagga cacagttatt ttataaactg ggaccggaag atgtattaty    420
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<210> 209
<211> 181
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (178)..(178)
<223> n equals a,t,g, or c

<400> 209

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ctgggggagc attgccattt atttctccat tttatttaca atgcacagta atggcatctt    120
tggcatcttc ccaaaccagt ttccatttgt tggtaatgca cgacattccc tgacccanaa    180
g                                                                    181
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<210> 210
<211> 612
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (47)..(47)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (534)..(534)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (537)..(537)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (563)..(563)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (565)..(565)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (591)..(591)
<223> n equals a,t,g, or c

<400> 210
cagtctgggc ttaagaaacc accagaagaa cccaaaccag aaatgcncaa gtgtaaatgc 60
aaaaattctt atagaagaaa tagcataaga atttgcacat tcggaaataa gaccaccttc 120
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tgtggccatt tatgattaag gcataatctc ctgttatggt ttcttctaca atagaatcca 480
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caaacaaatt ttgttttgaa atnangagtt cttctctcac ttccacagca nttattccct 600
gctataggga gg 612

<210> 211
<211> 1024
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (29)..(29)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (986)..(986)
<223> n equals a,t,g, or c

<400> 211
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gtctcctgtt aggacccaga tcttaatatt ggctagtgat aaacttgtaa ctgtttcaat 180
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<210> 212
<211> 366
<212> DNA
<213> Homo sapiens

<400> 212
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aaaaaa 366

<210> 213
<211> 519
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (371)..(371)
<223> n equals a,t,g, or c

<400> 213
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aaagcaaaaa taaagcatca tgtcttaatg gttttctaca aatcaacttc taattctaca 120
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gtctttccct nacatgcctg cctacactta accagatgtt ggttttcaat gtctaatttg 420
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<210> 214
<211> 2042
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2001)..(2001)
<223> n equals a,t,g, or c

<400> 214
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acggcactat gagaaaaaac attgatgttt ggaaaaagtg gaccacctta aatagcttgc   1080
agctacatgg cttacagctg cggattgcaa cacgcggggc tgaacagctg gctgaaggtg   1140
gaaggatggt gtattccacg tgttcactaa accctattga ggatgaagca gtcatagcat   1200
ctttactgga aaaaagtgaa ggtgctttgg agcttgctga tgtgtctaat gaactgccag   1260
ggctgaagtg gatgcctgga atcacacagt ggaaggtaat gacgaaagat gggcagtggt   1320
ttacagactg ggacgctgtt cctcacagca gacacaccca gatccgacct accatgttcc   1380
ctccgaagga cccagaaaag ctgcaggcca tgcacctgga gcgatgcctt aggatattac   1440
cccatcatca gaatactgga gggttttttg tggcagtatt ggtgaaaaaa tcttcaatgc   1500
cgtggaataa acgtcagcca aagcttcagg gtaaatctgc agagaccaga gaaagcacac   1560
agctgagccc tgcagatctc acagaaggga aacccacaga tccctctaag ctggaaagtc   1620
cgtcattcac aggaactggt gacacagaaa tagctcatgc aactgaggat ttagagaata   1680
atggcagtaa gaaagatggc gtgtgtggtc ctcctccatc aaagaaaatg aagttatttg   1740
gatttaaaga agatccattt gtatttattc ctgaagatga cccattattt ccacctattg   1800
agtaaggatt cagccttttt aattattcat ttaaagaaat ttactataga gtatcaaatg   1860
tacaactgat cacatgtaac cattgttttg tatgtagttc tgtctagctt tttttttttt   1920
ttaacctttt taactgcata ttagagcagg atgaaacttt agaggttact caatctttta   1980
atttaaggag aaagtaaaca nttactttgt gaacatgata gataaaaaaa aactggaccg   2040
gg                                                                  2042
```

<210> 215
<211> 308
<212> DNA
<213> Homo sapiens

<400> 215

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ggaggcagga ccttgtccta ttcattaatc ttgcccctca acagttattt tcagaggggc     60
aagaagtgtt tcagggttct tggcccttgt ttgaccagtc gtcctaaccc tcrtgtcttg    120
ggtcattgtt gttrtaatct ggggttacct tttggaaggt catggggtac ccttttgcaa    180
aagttatggg ccctmtcctt ggaaactgca cacacaccat gcagcttaca attcagggag    240
ttcacaggtc tacagaatcc tgggaaactc tccatgtccg gttctaatcc attgtagctt    300
cagtggga                                                             308
```

<210> 216
<211> 1568
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1550)..(1550)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1564)..(1564)
<223> n equals a,t,g, or c

<400> 216

```
ctcatcagcc ctatgaggta gggaggtagg tattattatc acccttgtta gttttttttgt    60
tttgttttgt tttccagatg agagaatcat tgctcacaga agtgaagtaa cttttccaag    120
gtcatacaat cagtaagtgg caggcaagga ctgaaatcca agttgttacc ctccaaagtc    180
```

```
cctgctctga gaactggagg aattctttat caaatctaaa atcctctttt agscctgtct    240
gctttaatat tccggtcttt attgatcctt ctcttctcta aamcttcagc tgtcagtata    300
aaaatcaagg aatttagcmc ttgttattgt gtgamcagct tcttgtctct cctgtactgt    360
aagtgggtct agggattttt attctttaaa tatccccctg tactcagtag atctttggga    420
gamcaagctc ataggcttct aataattctt tctttgactg ccagctgaat tagacagaag    480
gtaagtcctg ctgccgtgtc gtgcctaacc ccatctttat ttcctgtgct gttagagaac    540
agtcttttct tggctggaac aaatactaca gcctgctcaa ctagctaata tgtattgagt    600
tcttartatg ttccaaggac tgctctaagt attttatata tattaactca ctgaatctta    660
aataccctat gagctaagtc ctatttttat ccccatttta caaaagagga aactgaatgt    720
accagtgcat cagtatttga ctgagtaaat gaatgactgc tttgctgatg gatagtatta    780
ttagcaacaa ccctacaaat atgatgttat gtttgcatca tgcagtacag ctttatgtac    840
cttatgtcat tgtcactcat gattagcaaa taggcacgaa catccctatt ttatagaaga    900
ggaamccatg gctctaagag ggtgagtgat tctcaacagt cacatgccat ctgtatcctt    960
cagtaaacaa ggtatttggt ccattccagg atcgggggca agagagatgg gagggcctcg   1020
gtgagaaaca ctcatattca caaaaggtac tagatagata gacagataaa taaataaata   1080
gagataaaag ctagtaatag cagagatttg atgggaattc agatctttga ttcctagtcc   1140
agtgctcttt cttttatgta aggtgatggg aagcaagtct taggtccaga tctggcagct   1200
gctttgattt aggatcttaa gccagaagca gcagcgccct aaacaaaaag catcatttta   1260
acttctctgc atttctcaca ttctcaacaa tgaccatgcc ctactttcat aattaaaaac   1320
aaacaaataa acagaggggg caaaatgcat ccttctgagt gggctggggc ttgtagaggg   1380
attcttgggt ttgctctggg atgtctttgg gcccctgcac ttgtgggcac tctgatttat   1440
ccccacaggc cacctggccc accttatggg ctgaggaggg cttgatgggc ggaggsaagc   1500
agagctgagg agctggggag gagctggaaa ggactgctag aaggttccan tgaagctaca   1560
atgngtag                                                            1568
```

<210> 217
<211> 865
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (13)..(13)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (20)..(20)
<223> n equals a,t,g, or c

<400> 217

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accgcagcct gcngggctcn agcattccty tsgcytcagc ctcctgakta gctgggaccm     60
cagytccact aattttgaag ttttttkggt agacatgaag tctccctgtg ttgcccgggc    120
tggtctcaaa ctcctgacct caagcagtcc tcctgtcttg gcctctggaa atgctgggat    180
tacaggcgtg agccactgtg ctggcctctt ttttcttttt cttttttttt aaggttttta    240
tttgttaaat gggaagtctg tgccatcaac tgagcattgt attttctcct tagtaagagc    300
ctgggtgggc cactgggaga gaactataca ttaaatgtaa gtagcctctg ggtagagagc    360
ccctggctgg tttcctttcc tttctctcct tttctctact ttggtgtctg gaggcatttc    420
ccagactcca gtttcttacc accctcacgg attttgctat tgtattatca cctcctttat    480
cattcccaaa attgacttta tggagactca ttaaaagaaa gaatcatcgg ccgggagcgt    540
kgctcacgcc acgaaggcgg gcgaatcacc tgaggtgcgg agttcgtgac cagcctgacc    600
aaaacagaga aaccccatct ctactaaaca atacaaaatt agctgggcgt ggtggtgcac    660
gcctgtaatc ccagctactg ggaggctgg gacgggagaa tcacttgaac ccgggaggca     720
gaggttgcag tgaccaaaga tcgcactatt gcactccagc ctgggcaaca agagcaaaac    780
tctatctcaa aaaaaaaaa aaaaaaaaa aaaagggcgg ccgctctaga ggatccctcg      840
aggggcccaa gcttaggcgt gcatg                                          865
```

<210> 218
<211> 1687
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1568)..(1568)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1652)..(1652)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1654)..(1654)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1660)..(1661)
<223> n equals a,t,g, or c

<400> 218
ccacgcgtcc gggcagtggg gtgagggcac acaagcagtt cagggtccca gcaggaagtg 60
gggctgcagg gccggggtgg gtcctgggcc tggccatcag gcagcctagc aggttgttct 120
gggcatggag ggggcctggt gtggctgagg gcatgcccag ggctccctgg aggatcccgc 180
tctgtgccct gcccaccctg tgcctgggga gccctctgcc ctcacagccc acccacccca 240
ttttctatga ccacagagct ccgacctgga agatggctca cccaggaggt cccaggagct 300
ctcactcccc caggggacct ggaggacacc cagctctcag acaaaggctg ccttgccggc 360
gggggggagcc cgaaacagcc ctttgcagct ctgcaccagg agcaggtttt gcggaacccc 420
catgtaaggc ttccccgggg tggggtcctc ccagccgtgg gcctcagggt gaccgatcac 480
agggagagtg gctccctgcc ctgggcaccc cctgcggtgg ccccgacgac agctgaggag 540
tgaccacaag gtctctgccc acagtgctcg ggtgcggtg tctgggctgc gaagtggatc 600
cccctccttt cttgggcact gcagcagctt gggggcttt ttggacgtgg atgtgcctgg 660
tcctggtttc ccgagggcct ttacagtgga tgaggaggtg aacacaggga gtcctgagag 720
caagcaccac ctcgggcttt ggtgtagaaa caatggcccg gaccccaggc cggagccgtg 780
gcttggcctc ctgggtgtgt cttggcatct gaaatgcagg ctacccacac cggctcacct 840
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cctcgcctcc caaccagtct gcagttacag gggccagtgg atgggcgggt gagaaggacg 960
ggttccctca ggggagccgg ccggagcccg agccttcccc cttctccagg acgcaggcct 1020
gagcagcggg gagccgcccg agaaggagcg gcggcgcctc aaagagagtt ttgagaacta 1080
ccgcaggaag cgcgccctca ggaagatgca gaaaggatgg cggcagggtg gaggaggacc 1140
gggagaacac cacgggcagc gacaacaccg acactgaggg ctcctagccg cagcagccgc 1200
aggccccgac cagggcacac ccaccggccc ggcctcctgc cacccggggg tgccgacgcc 1260
ctggggcgca gacttccccg agccgtcgct gacttggcct ggaacgagga atctggtgcc 1320
ctgaaaggcc cagccggact gccgggcatt ggggccgttt gttaagcggc actcattttg 1380
cggaggccat gcgggtgctc accaccccca tgcacacgcc atctgtgtaa cttcaggatc 1440
tgttctgttt caccatgtaa cacacaatac atgcatgcat tgtattagtg ttagaaaaca 1500
cagctgcgta aataaacagc acgggtgacc cgcaaaaaaa aaaaaaaaaa aaaaaaaaaa 1560
aaaaaaanaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa ananaaaaan naaaaaaaaa aaaaaaaaaa 1680
aaaaaaa 1687

<210> 219
<211> 570
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (5)..(5)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (16)..(16)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (496)..(496)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (523)..(523)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (531)..(531)
<223> n equals a,t,g, or c

<400> 219
ttccngtgcc actatngaat gtacgcctgc aggtaccggt ccggaattcc cgggtcgacc 60
cacgcgtccg ggcagtgggg tgagggcaca caagcagttc agggtcccag caggaagtgg 120
ggctgcaggg ccggggtggg tcctgggcct ggccatcagg cagcctagca ggttgttctg 180
ggcatggagg gggcctggtg tggctgaggg catgcccagg gctccctgga ggatcccgct 240
ctgtgccctg cccaccctgt gcctggggag ccctctgccc tcacagccca cccaccccat 300
ttwctatgac cacagagctc cgacctggaa gatggctcac ccaggaggtc ccaggagctc 360
tcactccccc aggacctgga rgacacccag ctctcagaca aargctgcct tgccggcggg 420
gggagcccga aacagccctt tgcagctctg caccaggagc aggttttgcg gaaccccccat 480
gtaaggcttc cccggngtgg ggtcctccag ccgtgggcct canggtgacc natcacaggg 540
agagtggctc cctgtcctgg gcacccccctg 570

<210> 220
<211> 1752
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1099)..(1099)
<223> n equals a,t,g, or c

<400> 220
aaggtacgcc tgcaggtacc ggtccggaat tcccgggtcg acccacgcgt ccgtccagga 60
cagagagtgc acaaactacc cagcacagcc ccctccgccc cctctggagg ctgaagaggg 120
attccagccc ctgccaccca cagacacggg ctgactgggg tgtctgcccc ccttgggggg 180
gggcagcaca gggcctcagg cctgggtgcc acctggcacc tagaagatgc ctgtgccctg 240
gttcttgctg tccttggcac tgggccgaag cccagtggtc ctttctctgg agaggcttgt 300
ggggcctcag gacgctaccc actgctctcc gggcctctcc tgccgcctct gggacagtga 360
catactctgc ctgcctgggg acatcgtgcc tgctccgggc cccgtgctgg cgcctacgca 420
cctgcagaca gagctggtgc tgaggtgcca gaaggagacc gactgtgacc tctgtctgcg 480
tgtggmtgtc cacttggccg tgcatgggca ctgggaagag cctgaagatg aggaaaagtt 540
tggaggagca gctgacttag ggtggagga gcctaggaat gcctctctcc aggcccaagt 600
cgtgctctcc ttccaggcct accctactgc ccgctgcgtc ctgctggagg tgcaagtgcc 660
tgctgccctt gtgcagtttg gtcagtctgt gggctctgtg gtatatgact gcttcgaggc 720
tgccctaggg agtgaggtac gaatctggtc ctatactcag cccaggtacg agaaggaayt 780
caaccacaca cagcagctgc ctgactgcag ggggctcgaa gtctggaaca gcatcccgag 840
ctgctgggcc ctgccctggc tcaacgtgtc agcagatggt gacaacgtgc atctggttct 900
gaatgtctct gaggagcagc acttcggcct ctccctgtac tggaatcagg tccagggccc 960
cccaaaaccc cggtggcaca aaaacctgac tggaccgcag atcattacct tgaaccacac 1020

agacctggtt ccctgcctct gtattcaggt gtggcctctg gaacctgact ccgttagacg 1080
aacatctgcc ccttcaggna ggacccccgc gcacaccaga acctctggca agccgcccga 1140
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gcggcactgt gctggcgggc tccgggtggg gacccctgcc agccactggt cccaccgctt 1260
tcctgggaga aygtcactgt ggacaaggtt ctcgagttcc cattgctgaa aggccaccct 1320
aacctctgtg ttcaggtgaa cagctcggag aagctgcagc tgcaggagtg cttgtgggct 1380
gactccctgg ggcctctcaa agacgatgtg ctactgttgg agacacgagg cccccaggac 1440
aacagatccc tctgtgcctt ggaacccagt ggctgtactt cactacccag caaagcctcc 1500
acgagggcag ctcgccttgg agagtactta ctacaagacc tgcagtcagg ccagtgtctg 1560
cagctatggg acgatgactt gggagcgcta tgggcctgcc ccatggacaa atacatccac 1620
aagcgctggg ccctcgtgtg gctggcctgc ctactctttg cctgcgcttt ccctcatcct 1680
ccttctcaaa aaggatcacg cgaaagggtg gctgaggctc ttgaaacagg acgtccgctc 1740
gggggcggcc gc 1752

<210> 221
<211> 536
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (508)..(508)
<223> n equals a,t,g, or c

<400> 221
ggtcgaccca cgcgtccgcc cacgcgtccg gcttccttaa tgtaatttaa accctggcaa 60
acattcttta gaaaccaaga ggaaagaaag aacaaatatc aaaaaagaca tagaatttaa 120
tattgataca atttcacctc taaaatggat ttgaagaaat gcaactttat atcaaaaaat 180
gtcatctgat ttcctttgtt tctttttaa attatgtaat cagatgattt tatgtttttt 240
tttcagggga gcggaatatt ggtttctttt acttgttgtt ttcagttttc tctgccattc 300
atgtttcttt tttgtgttca gtgtttcaaa tacaatttgt atttaaggat tttaaaatac 360
caaactgtaa ctgagtacag tggatcgttt tctgttagga tgttaatatt atacaatgaa 420
atctataaag tgttgtcaat ttgattattg acacatataa catgtttaca aataaactgt 480
ggtattgatc aaaaaaaaaa aaaaaaancc cggggggggc cccggaaccc aatccc 536

<210> 222
<211> 2409
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (694)..(694)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (716)..(716)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (755)..(755)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (761)..(761)
<223> n equals a,t,g, or c

<220>

<221> misc_feature
<222> (791)..(791)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (808)..(808)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (880)..(880)
<223> n equals a,t,g, or c

<400> 222
ccacgcgtcc ggcgagacgc gttcaccacc atatgcactg ttgtcaactc ccctggagat 60
gcgcccaagc cccacaggaa gccttcctcc tctgcctcct cttcctcatc ctcgtcctcg 120
ttctccttgg atgcagccgg ggcctccctg gccacactcc ctggaggctc catcctgcag 180
ccgcggccct ccttgcccct ctcctccacg atgcacttgg ggcctgtggt ttccaaggcc 240
ctgagtacct cttgccttgt ttgctgcctc tgccaaaacc cggccaactt caaggacctt 300
ggggacctct gtgggcccta ctaccctgaa cactgcctcc ccaaaaagaa gccaaaactc 360
aaggagaagg tgcggccaga aggcacctgt gaggaggcct cgctgccgct tgagagaaca 420
ctcaaaggtc ccgagtgtgc agctgccgcc actgccggga agccccccag gcctgacggc 480
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gacaagggtc gcaaacatga gtgcagcaag gaggctccgg cagagcccgg cggggaggcc 660
caggagcact gggtgcatga ggcctgtgcc gtgnggaccg gcggcgtcta cctggnggcc 720
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tgccaagaag ncggggccac catcgggngc tgccacaaag gatgcctcca cacctaccac 840
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cccaaacata agaggctgcc gtagtaatcc accccaacgg ccggaggagc cgccggagcc 960
cgcctgcccg cccgccgccg aaggagagga gccgcctgcg cagcccccgg gcctttgagc 1020
tgctcccagc gctggtccag agccgatcct tgatccgggt cccggatcgt ggatccggcc 1080
gcctagggct cagacttgcg gccccgggtt gggaggaaaa cccgttccgg agccgcctgc 1140
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tgggtgctgc cgccacccca gtcggtcgtg gcgtgcagct gggagccctg ggcttggggg 1380
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cgtgcggttc gggcaaagcc ggggtagacc tgggctatgc tcagttaggg gttgcgggat 1620
ccccgagtgt gggcgggact gggacaccct ttggcctctg tttgtcccct ttccagtcct 1680
ccaccccacc cctggagccc agcctgggag cgcaaaaccc aagaagcggc cagaacgcac 1740
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cacgggagca gggacagcgc tagatttcgt gtacaaaacc tgtgtacccc tctatatata 1860
tgttacatag aatgtatata tgttgggaac atgctcgctt ctcccgtgtg tcgccgccgt 1920
gcgtcgtgcg cccgcaacag agccccaacc gggcctttgc cgggtaaggg gctaccgcga 1980
cgccacttgt ccacgcagcc accaccggcc cgggccagtc cctgccagtc cgtccgcctg 2040
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ggccgcccta gcaacttcct gtacatatga ctgtaaaatg gtaaacgtgt gtattatatc 2160
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gtgtatcgag ctgtttctaa aagatgttta ttttccttaa gagtaaaaaa cagtcattgc 2340
attcagaaaa aaaaaaaaaa aaaaagtcaa taaagataca acgattgttt tggaaaaaaa 2400
aaaaaaaaa 2409

<210> 223
<211> 737
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (21)..(21)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (369)..(369)
<223> n equals a,t,g, or c

<400> 223
nagagggaag agagaaaaag ntacaatgct tcgccgtycg sctktmcgkc csygtcctca 60
gctctgtcca cgcttcgata ggcctgacgc agcccccagc ccagggccgc cctagcaact 120
tcctgtacat atgactgtaa aatggtaaac gtgtgtatta tatctggcct cgttatatag 180
tgtatatata tgtatacata tacatatata taatatatat gaagactgta aatgttaaga 240
cgactagtgt tcttattagt atattgcttc acactgaaga ttgtgtgtat cgagctgttt 300
ctaaaagatg tttattttcc ttaagagtaa aaaacagtca ttgcattcag aaaaaaaaaa 360
aaaaaaaang tcaataaaga tacaacgatt gttttggaaa atctgcagcc cgtggattcc 420
gaccagattc agctgggagc cgggccaggc tttaggttgg ggaatgggaa tgaagggagg 480
ggctgggggg gggggcatga atggagtcag ggagtcggcc tttcacagaa caggaaacct 540
cccccgcccc tgtgcccccct ctccagtgtg gcggcaggtc gggagggagg aggcttcttt 600
gctgtgagat gaccaggggc cgggatgggg gaggtgagac gtgccagact tcttgcaggg 660
agacccaagc tgtagctcct gtcccacaac aggtcctgga agtcagtcca tcctcccgtg 720
ccacccaggg acctaat 737

<210> 224
<211> 1471
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (798)..(798)
<223> n equals a,t,g, or c

<400> 224
tttctgaatg caatgactgt tttttactct taaggaaaat aaacatcttt tagaaacagc 60
tcgatacaca caatcttcag tgtgaagcaa tatactaata agaacactag tcgtcttaac 120
atttacagtc ttcatatata ttatatatat gtatatgtat acatatatat acactatata 180
acgaggccag atataataca cacgtttacc attttacagt catatgtaca ggaagttgct 240
agggcggccc tgggctgggg gctgcgtcag gcctatcgaa gcgtggacag agctgaggac 300
acggacggac aggcggacgg actggcaggg actggcccgg gccggtggtg gctgcgtgga 360
caagtggcgt cgcggtagcc ccttacccgg caaaggcccg gttggggctc tgttgcgggc 420
gcacgacgca cggcggcgac acacgggaga agcgagcatg ttcccaacat atatacattc 480
tatgtaacat atatatagag ggtacacag gttttgtaca cgaaatctag cgctgtccct 540
gctcccgtgc agagtaggcg cggcggtccc tggtggtgca caacggtcgc gcgtccgccg 600
gagccggagg tgcgttctgg ccgcttcttg ggttttgcgc tcccaggctg ggctccaggg 660
gtggggtgga ggactggaaa ggggacaaac agaggccaaa gggtgtccca gtcccgccca 720
cactcgggga tcccgcaacc cctaactgag catagcccar gtctaccccg gctttgcccg 780
aaccgcacga gagatctngc aaargctggg cggraaggcc cctgracgcg ttccgcacgg 840
tttgttccaa aggctccggc ctytccagtg ccggcctagc ccgctctcag aaaggcttcc 900
tttctccycc gcctagtcca cggagctagg agccgccctc cgcctcttcc agtactgttt 960
cgaccccccac ccccaagccc agggctccca gctgcacgcc acgaccgact ggggtggcgg 1020
cagcacccac gtggaatgtg tgccacgtcg tcttgagatt ccagagggaa agtgtcccca 1080
ggacaaagcc gtctcccacc ctcgccggag gctgagcgcc ccggggagtc tggccgctcc 1140

gcgggctccc cctccgcaag cctggcccct ggggtgggca agaacgccct gtgccgtccg 1200
gttccgggag cagkcggctc cggaacgggt tttcctccca acccggggcc gcaagtctga 1260
gccctaggcg gccggatcca cgatccggga cccggatcaa ggatcggctc tggaccagcg 1320
ctgggagcag ctcaaaggcc cgggggctgc gcaggcggct cctctccttc ggcggcgsgc 1380
gggcaggcgg gctccggcgg ctcctmcgrc cgttggggtg gattactacg gcagcctctt 1440
atgtttggga catttcaaag gggaattctc t 1471

<210> 225
<211> 3302
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (3274)..(3274)
<223> n equals a,t,g, or c

<400> 225
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ggccctggag tccacgcgga ttttcgaagc tggggctggc aagaggccgc tggacaccac 120
gctccagtcg tcagcccact tcctagctga acagcgcgag gcggcggcag cgagccgggt 180
cccaccatgg ccgcgaatta ttccagtacc agtacccgga gagaacatgt caaagttaaa 240
accagctccc agccaggctt cctggaacgg ctgagcgaga cctcgggtgg gatgtttgtg 300
gggctcatgg ccttcctgct ctccttctac ctaattttca ccaatgaggg ccgcgcattg 360
aagacggcaa cctcattggc tgaggggctc tcgcttgtgg tgtctcccga cagcatccac 420
agtgtggctc cggagaatga aggaaggctg gtgcacatca ttggcgcctt acggacatcc 480
aagcttttgt ctgatccaaa ctatggggtc catcttccgg ctgtgaaact gcggaggcac 540
gtggagatgt accaatgggt agaaactgag gagtccaggg agtacaccga ggatgggcag 600
gtgaagaagg agacgaggta ttcctacaac actgaatgga ggtcagaaat catcaacagc 660
aaaaacttcg accgagagat tggccacaaa aaccccagtg ccatggcagt ggagtcattc 720
ayggcaacag ccccctttgt ccaaattggc aggtttttcc tctcgtcagg cctcatcgac 780
aaagtcgaca acttcaagtc cctgagccta tccaagctgg aggaccctca tgtggacatc 840
attcgccgtg gagacttttt ctaccacagc gaaaatccca agtatccaga gktgggagac 900
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cacgtggtca ctgtgattgc ccggcagcgg ggtgaccagc tagtcccatt ctccaccaag 1020
tctggggata ccttactgct cctgcaccac ggggacttct cagcagagga ggtgtttcat 1080
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ttggagtgaa aagaccctgg cacccgcccg acacctgcgt gagccctagg atccaggtcc 1440
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cacyccctct cctcttcagg ggccagactt ggcagcatgt gcaccaggtt ggtgttcacc 1560
agctcatgtc ttccccacat ctcttcttgc cagtaagcag ctttggtggg cagcagcagc 1620
tcatgaatgg caagctgaca gcttctcctg ctgtttcctt cctctcttgg actgagtggg 1680
tacggccagc cactcagccc attggcagct gacaacgcag acacgctcta cggaggcctg 1740
ctgataaagg gctcagcctt gccgtgtgct gcttctcatc actgcacaca agtgccatgc 1800
tttgccacca ccaccaagca catctgtgat cctgaagggc ggccgttagt cattactgct 1860
gagtcctggg tcaccagcag acacactggg catggacccc tcaaagcagg cacacccaaa 1920
acacaagtct gtggctagaa cctgatgtgg tgtttaaaag agaagaaaca ctgaagatgt 1980
cctgaggaga aaagctggac atatactggg cttcacactt atcttatggc ttggcagaat 2040
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aaggatttgt tttcactctg ggaggagagg gtggagaaag cacttgcttt catcctctgg 2400
catcggaaac tcccctatgc acttgaagat ggtttaaaag attaaagaaa cgattaagag 2460
aaaaggttgg aagctttata ctaaatgggc tccttcatgg tgacgccccg tcaaccacaa 2520
tcaagaactg aggcctgagg ctggttgtac aatgcccacg cctgcctggc tgctttcacc 2580

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tgggagtgct ttcgatgtgg gcacctgggc ttcctagggc tgcttctgag tggttctttc   2640
acgtgttgtg tccatagctt tagtcttcct aaataagatc cacccacacc taagtcacag   2700
aatttctaag ttccccaact actctcacac ccttttaaag ataaagtatg ttgtaaccag   2760
gatgtcttaa atgattcttt gtgtaccttt tctgtcatat tcagaaaccg ttttgtgcct   2820
gctgggagta attcctttag caattaagta tttggtagct gaataagggg tcagaacttc   2880
tgaaaccaga gatctgtaat catctctatt ggcctggggt gcctgtgcta taaatgagtt   2940
tcttcacatg aaaaacacag ccagcccaag atgacttatc tgggtttagg attcaatagt   3000
attcactaac tgcttattac atgagcaatt tcatcaaatc tccaaactct taaaggatgc   3060
tttcggaaaa cacgctgtat acctagatga tgactaaatg caaaatcctt gggctttggt   3120
ttttttctag taaggatttt aaataactgc cgacttcaaa agtgttctta aaacgaaaga   3180
taatgttaag aaaaatttga aagctttgga aaaccaaatt tgtaatatca ttgtattttt   3240
tattaaaagt tttgtaataa atttctaaat tatnaaaaaa aaaaaaaaaa aaaaaaaaaa   3300
aa                                                                  3302

<210> 226
<211> 2227
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (289)..(289)
<223> n equals a,t,g, or c

<400> 226
cggacgcgtg ggtcgaccca cgcgtccggg aaaaarggaa aaratgccgt gtaaaatctc     60
gttctgtgtc tgaattgccg taggctcaga tcttcatttg aggttctgtg tctgaattgc    120
cgtaggctca gatcttcatt tgaggttatg ttctataagt taacgttgat cttgtgtgag    180
ctttcggtag ctggagtaac acaggcggcc tcacagcgac ctctccagcg ccttccaagg    240
cacatctgca gccagcgtaa tcctcctggg agatgcctcc tcaaggccnt gctccagacc    300
acgtggggar ggcctgacar ccaattccca ggctgtcccc acccttgrag agtgacccta    360
aacgctagac agatggggaa tgggaaagaa aagaaagctg cagacctcaa gttaaaattc    420
cctcaaaaac gtttttattt atctgctttt tctgaaagga taaaggcttt ttgaaaatta    480
ttttctaaca aataacatga acacttctag aaaccctaga aaaacacaaa gtattcaaaa    540
tagaaagaaa aattacccat tactctttaa gccagcatta tccattgcgg tgcttttgga    600
gttgggtgag gccgtagcct ctgccaagtc aaggagcccg gtggtggctg tggcattcct    660
gcagggttgt tttttttttct ttgagatgga gtctcactct tgtcacccca gctggaatgt    720
ggtggtgtaa acagctcact gcagccttga ccctgaggct caagcgatcc ttctgccttg    780
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gtcttgatat gcgaggacgc tgtgtcttcc ctgccacatt ttcttcttct ttcttgagac    900
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tcgaccctca ggctcaagcg atcctcacgc ctcggacccc caaagtgctg ggatcacagg   1020
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tarccatscc tgtttcaaga gtgtaggtgg tcaccctgtc tctgycgctg acctggcctg   1140
gaccctcggc tgtgagaggg aggggtgggc tgggctggag gaacctraag ccctcgtgat   1200
gtcacaagcc catctggctg ggcatcccct gctgtgtcct gagctgcaca tgccccaggt   1260
ggcccccaca gcagaggcga gccactgrag ggtgragggc ttccacggac ggtcttcagg   1320
ggragaagaa gggcccaggc cccaggaga ctcaggagac cagagcctgg ggtcaggggc   1380
tyagcagggg ctyarccagg gctggatgtc cggagccagc cccgmagccc tgkgktcttt   1440
gttcttcgca ctcccaccgt ccgtgtgaac agctccagcc ccacctgcgc ctccctgtgc   1500
tgggctccat cagggagccc agaagacgtg tgtgcttctg aaattgggtc cctacatgcc   1560
tttgtcccag tgcaccttgc tccttccatt tactatcgag atttaaatgc ctgttttctc   1620
cccagaggtt gacggatata ttcagacgtt acgacacgga tcaggacggc tggattcagg   1680
tgtcgtacga acagtacctg tccatggtct tcagtatcgt atgaccctgg cctctcgtga   1740
agagcagcac aacatggaaa gagccaaaat gtcacagttc ctatctgtga gggaatggag   1800
cacaggtgca gttagatgct gttcttcctt tagattttgt cacgtgggga cccagctgta   1860
catatgtgga taagctgatt aatggtttg caactgtaat agtagctgta tcgttctaat   1920
gcagacattg gatttggtga ctgtctcatt gtgccatgag gtaaatgtaa tgtttcaggc   1980
attctgcttg caaaaaaatc tatcatgtgc ttttctagat gtctctggyt ctatagtgca   2040
aatgctttta ttagccaata ggaattttaa aataacatgg aacttacaca aaaggctttt   2100
catgtgcctt actttttaa aaaggagttt attgtattca ttggaatatg tgacgtaagc    2160
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aataaaggga atgttagacg tgtaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2220
aaaaaaa 2227

<210> 227
<211> 2214
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (289)..(289)
<223> n equals a,t,g, or c

<400> 227
cggacgcgtg ggtcgaccca cgcgtccggg aaaaarggaa aaratgccgt gtaaaatctc 60
gttctgtgtc tgaattgccg taggctcaga tcttcatttg aggttctgtg tctgaattgc 120
cgtaggctca gatcttcatt tgaggttatg ttctataagt taacgttgat cttgtgtgag 180
ctttcggtag ctggagtaac acaggcggcc tcacagcgac ctctccagcg ccttccaagg 240
cacatctgca gccagcgtam tcctcctggg agatgcctcc tcaaggccnt gctccagacc 300
acgtgggrar ggcctgacaa gccaattccc aggctgtccc cacccttgra gagtgaccct 360
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ccctcaaaaa cgtttttatt tatctgcttt ttctgaaagg ataaaggctt tttgaaaatt 480
atttctaac aaataacatg aacacttcta gaaaccctag aaaaacacaa agtattcaaa 540
atagaaagaa aaattaccca ttactcttta agccagcatt atccattgcg gtgcttttgg 600
agttgggtga ggccgtagcc tctgccaagt caaggagccc ggtggtggct gtggcattcc 660
tgcagggttg tttttttttc tttgagatgg agtctcactc ttgtcacccc agctggaatg 720
tggtggtgta aacagctcac tgcagccttg accctgaggc tcaagcgatc cttctgcctt 780
ggcctcctga gtagctggga tcccaggcga gagtcaccac accctgtcca tgttcctgca 840
ggtcttgata tgcgaggacg ctgtgtcttc cctgccacat tttcttcttc tttcttgaga 900
cagacccttg ctccatcacc caggccagag tgtggtsgtg cgaacacggc tcactgcagc 960
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tarccatscc tgtttcaaga gtgtaggtgg tcaccctgtc tctgccgctg acctggcctg 1140
gaccctcggc tgtgagaggg aggggtgggc tgggctggag gaacctraag ccctcgtgat 1200
gtcacaagcc catctggctg ggcatcccct gctgtgtcct gagctgcaca tgccccaggt 1260
ggcccccaca gcagaggcga gccactgrag ggtgragggc ttccacggac ggtcttcagg 1320
ggragaagaa gggcccaggc ccccaggaga ctcaggagac cagagcctgg ggtcaggggc 1380
tmagcagggg ctyarccagg gctggatgtc cggagccagc cccgmagccc tgkgktcttt 1440
gttcttcgca ctcccaccgt ccgtgtgaac agctccagcc ccacctgcgc ctccctgtgc 1500
tgggctccat cagggagccc agaagacgtg tgtgcttctg aaattgggtc cctacatgcc 1560
tttgtcccag tgcaccttgc tccttccatt tactatcgag atttaaatgc ctgttttctc 1620
cccagaggtt gacggatata ttcagacgtt acgacacgga tcaggacggc tggattcagg 1680
tgtcgtacga acagtacctg tccatggtct tcagtatcgt atgaccctgg cctctcgtga 1740
agagcagcac aacatggaaa gagccaaaat gtcacagttc ctatctgtga gggaatggag 1800
cacaggtgca gttagatgct gttcttcctt tagattttgt cacgtgggga cccagctgta 1860
catatgtgga taagctgatt aatggttttg caactgtaat agtagctgta tcgttctaat 1920
gcagacattg gatttggtga ctgtctcatt gtgccatgag gtaaatgtaa tgtttcaggc 1980
attctgcttg caaaaaaatc tatcatgtgc ttttctagat gtctctggtt ctatagtgca 2040
aatgctttta ttagccaata ggaattttaa aataacatgg aacttacaca aaaggctttt 2100
catgtgcctt actttttaa aaaggagttt attgtattca ttggaatatg tgacgtaagc 2160
aataaaggga atgttagacg tgtaaaaaaa aaaaaaaaaa aaaaaaaaaa aaag 2214

<210> 228
<211> 1145
<212> DNA
<213> Homo sapiens

<400> 228
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attacaaaag acttcccttt tcttggggta tggctgtctc agcacaatac tcaacataac 120
tgcagaactg atgtggctca ggcaccctgg ttttaattcc ttgaggatct ggcaattggc 180

ttacgcaaaa ggtcaccatt tgaggtcctg ccttactaat tatgtgctgc ccaacaacta 240
aatttgtaat ttgtttttct ctagtttgag cagggtctga atttttttcat ttatttcctt 300
ttttgccagc agacagactt gagtctgtaa agacaagcaa atacactgac agaagtttac 360
catagtttct aaaatgtaaa aaagaaaacc cccaaaagac tcaagaaaat tagaccacaa 420
attttgcatt gttcattgta gcactattgg taataaaata acaaatgttt gtgcattttt 480
atgtgaagat ccttctcgta tttcatttgg aaagatgagc aagaggtctg cttccttcat 540
tttacttccc cttctgtttt tgaaaggcag tttcgccaag cttaatgcaa gaatatctga 600
ctgtttagaa gaaagatatt gccacaatct ctggatggtt ttccagggtt gtgttattac 660
tgagcttcat ctttccagaa tgagcaaaac actgtccagt ctttgttacg attttgtaat 720
aaatgtgtac attttttttta aatttttgga catcacatga ataaaggtat gtatgtacga 780
atgtgtatat attatatata tgacatctat tttggaaaat gtttgccctg ctgtacctca 840
tttttaggag gtgtgcatgg atgcaatata tgaaaatggg acattctgga actgctggtc 900
aggggacttt gtcgccctgt gcactaaaag ggccagattt tcagcagcca aggacatcca 960
tacccaagtg aatgtgatgg gacttaaaag aagtgaactg agacaattca ctctggctgt 1020
ttgaacagca gcgtttcata ggaagagaaa aaaagatcaa tcttgtattt tctgaccaca 1080
taaaggcttc ttctctttgt aataaagtag aaaagctctc ctcaaaaaaa aaaaaaaaaa 1140
aaaaa 1145

<210> 229
<211> 802
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (337)..(337)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (359)..(359)
<223> n equals a,t,g, or c

<400> 229
ggtgggtgac cagagagtcc tgtctatcct aggaggagaa cattcagccc aaatcccagc 60
cccatcatgc acagatcaga gccatttctg aaaatgtcgc tgctgattct gcttttcctg 120
ggattggcag aagcctgtac tcctcgtgaa gtcaacttgc tgaaagggat cataggtctc 180
atgagcagac tgtcaccgga tgagatccta ggcttgctga gcctccaagt actgcatgaa 240
gaaacaagtg gctgcaagga ggaagttaaa cccttctcag gcaccacccc atccaggaaa 300
ccactcccca agagggaaga acacgtggaa yttcctngaa atgcgsctac atggtgrtng 360
acctacctct tcgtatccta caacaaaggg gactggttca ctttttcctc ccaagtgtta 420
ctgccaytac tgtaacttgg aactggacat cagggatgat ccctgctgtt ctttctagtg 480
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aggaatggca cctgggtgcc cagaggcatg gccagaaggt gtctgtgggg gccatgcctt 660
agggggatgc acccagggcg gctgagagag caactgcagg agtttcccct aaaatctctc 720
ctccagatcg ttctcgaact ttccccacta cttccataat aaaatgtata cttgttgaaa 780
aaaaaaaaaa aaaaaactcg ag 802

<210> 230
<211> 711
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (345)..(345)
<223> n equals a,t,g, or c

<400> 230
ggcacgagcg aagaccctgt tcggaccctg ccccgattcc agactcaggt agatcgtcgg 60

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catacccctct accgtggaca ccaggcagcc ctggggctga tggagagaga tcaggtatcc     120
cccagggagt aggggctacc ttgaggggat gatagacctc ccccactccc agtgkkactc     180
tggaaatatg aaggaactag ggagtggaag agatttcaga gctggggaga ggagttcctc     240
ccttcaaagc cagcaactgc ctttggggaa tgtcgggggg tctctccttt ctcctgcttg     300
tttraggtgg tacacagtcc ccccttcamc tggsgggaag ctgtnccgga caractcatc     360
tcagctttcc cttggggcag gatcgggggc agcagctcca gcagaaacag caggatctgg     420
agcaggaagg cctcgaggcc acacaggggc tgctggccgg cgagtgggcc ccacccctct     480
ggragctggg cagcctcttc caggccttcg tgaagaggga gagccaggct tatgcgtaag     540
cttcatagct tctgctggcc tggggtggac ccaggacccc tggggcctgg gtgccctgag     600
tggtggtaaa gtggagcaat cccttcacgc tccttggcca tgttctgagc ggccagcttg     660
gcctttgcct taataaatgt gctttatttt caaaaaaaaa aaaaaaaaac t              711
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<210> 231
<211> 1614
<212> DNA
<213> Homo sapiens

<400> 231

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ggtgattggt agttactatg tggggacaca attacttggg ctgaaataat ccacctgttg      60
tggttggggt cctctggggc attccagggt gagaggttgt cactgccacc tgggccatgt     120
gggccggcac cagcattttg tggttacgaa ttctacagtc acaaatatct ttgggcaaat     180
ccccttctat acctcaaggc agcttttggt ttgcaacccc actggccaga gggaagggcc     240
agtcacttgg ctctctcact gccctgcgcc ccagatggtt ctagggctgc tgttttccct     300
tggccctgcc aacaccactg tttttacttc tgctcattgg ctgagtgcag tggttcctgg     360
aagccagtgg cacgtttccc cgcgtagctc gcttatccca cagcacacac ccaagggttc     420
tgttgctaac acgctgaatt aattctttgc tcatcttaca gagtgtgttt tgactgcccc     480
catttctgag gccttgtaag gccagagctt tgttgcttca tcggcaggtt gggacttaga     540
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tggaggctga agttgaagcg aggctgtgag gggagatgga cgtgtgagga gggatgatgg     660
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<210> 232
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<212> DNA
<213> Homo sapiens

<220>
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<222> (14)..(14)
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<220>
<221> misc_feature
<222> (55)..(55)
<223> n equals a,t,g, or c

<220>
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<222> (63)..(64)
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<220>
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<222> (174)..(174)
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<400> 232
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<210> 233
<211> 1191
<212> DNA
<213> Homo sapiens

<400> 233
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<210> 234
<211> 1626
<212> DNA

<213> Homo sapiens

<220>
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<222> (525)..(525)
<223> n equals a,t,g, or c

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<221> misc_feature
<222> (542)..(542)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (562)..(562)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (607)..(607)
<223> n equals a,t,g, or c

<400> 234
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<211> 2351
<212> DNA
<213> Homo sapiens

<400> 235
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ccagagaaca gggctcccca ttacaatctt ttcgagatct tttcccttgc taaccggatc 180

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<210> 236
<211> 1001
<212> DNA
<213> Homo sapiens

<400> 236

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<210> 237
<211> 669
<212> DNA
<213> Homo sapiens

<400> 237
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<210> 238
<211> 417
<212> DNA
<213> Homo sapiens

<400> 238
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<210> 239
<211> 1949
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1948)..(1948)
<223> n equals a,t,g, or c

<400> 239
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<210> 240
<211> 1487
<212> DNA
<213> Homo sapiens

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<222> (78)..(78)
<223> n equals a,t,g, or c

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gatgggatgg ctgcacggcg tggtgaaggt actgaacgcc acctcactgt aagacggtag    1380
atttgtatt ttaccacaat aaacaaaaca aaacaaaacc aaaaaaaaa aaaaaaaaa       1440
aaaaaaaagg aattcgatat caagcttatc gataccgtcg acctcga                  1487
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<210> 241
<211> 1525
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (78)..(78)
<223> n equals a,t,g,. or c

<400> 241

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ccgcctggct cctgctgnca cctgcaggct cgtcgcgggt ggagcccacc caagacatca     120
gcatcagcga ccagctgggg ggccaggacg tgcccgtgtt ccggaacctg tccctgctgg     180
tggtgggtgt cggcgccgtg ttctcactgc tattccacct gggcacccgg gagaggcgcc     240
ggccgcatgc ggasgagcca ggcgagcaca ccccctgtt ggcccctgcc acggcccagc      300
ccctgctgct ctggaagcac tggctccggg agcsggcttt ctaccaggtg ggcatactgt     360
acatgaccac caggctcatc gtgaacctgt cccagaccta catggccatg tacctcacct     420
actcgctcca cctgcccaag aagttcatcg cgaccattcc cctggtgatg tacctcagcg     480
gcttcttgtc ctccttcctc atgaagccca tcaacaagtg cattgggagg aacatgacct     540
acttctcagg cctcctggtg atcctggcct ttgccgcctg ggtggcgctg gcggagggac     600
tgggtgtggc cgtgtacgca gcggctgtgc tgctgggtgc tggctgtgcc accatcctcg     660
tcacctcgct ggccatgacg gccgacctca tcggtcccca cacgaacagc ggactktcgt     720
gtacggctcc atgagcttct tggataaggt ggccaatggg ctggcagtca tggccatcca     780
gagcctgcac ccttgcccct cagagctctg ctgcagggcc tgcgtgagct ttaccactg      840
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cctgctgtgg ccgacccgcc tgcgacgctg ggaccgtgat gcccggccct gactcctgac     960
agcctcctgc acctgtgcaa gggaactgtg ggacgcacg aggatgcccc ccarggcctt     1020
ggggaaaagc cccactgcc cctcactctt ctctggaccc ccaccctcca tcctcaccca     1080
gctcccgggg gtggggtcgg gtgagggcag cagggatgcc cgccagggac ttgcaaggac    1140
cccctgggtt ttgagggtgt cccattctca actctaatcc atcccagccc tctggaggat    1200
ttggggtgcc cctctcggca gggaacagga agtaggaatc ccagaagggt ctgggggaac    1260
cctaaccctg agctcagtcc agttcacccc tcacctccag cctgggggtc tccagacact    1320
gccagggccc cctcaggacg gctggagcct ggaggagaca gccacggggt ggtgggctgg    1380
gcctggaccc caccgtggtg ggcagcaggg ctgcccggca ggcttggtgg actctgctgg    1440
cagcaaataa agagatgacg gcaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa    1500
aaaaaaaaaa aaacccaccg tccgc                                          1525
```

<210> 242
<211> 1050
<212> DNA
<213> Homo sapiens

<400> 242

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ccacgcgtcc ggccagccag tccgcccgtc cggagcccgg ctcgctgggg cagcatggcg      60
gggtcgccgc tgctctgggg gccgcgggcc gggggcgtcg gcctttttggt gctgctgctg    120
ctcggcctgt ttcggccgcc ccccgcgctc tgcgcgcggc cggtaaagga gccccgcggc     180
ctaagcgcag cgtctccgcc cttggctaga ctggcgctcc tcgccgcttc cggcggtcag     240
tgccccgagg tgaggcggcg ggggcggtgc agacctggcg cgggcgctgg cgcatctgct     300
ggagccgaac gtcaggagcg ggcgcgggcc gaggcgcaga ggctgaggat cagcaggcgc     360
gcgtcctggc gcagctgctg cgcgtctggg gcgccccccg caactctgat ccggctctgg     420
gcctggacga cgaccccgac gcgcctgcag cgcagctcgc tcgcgctctg ctccgcgccc     480
gccttgaccc tgccgcccta gcagcccagc ttgtccccgc gcccgtcccc gccgcggcgc     540
tccgaccccg gcccccggtc tacgacgacg gccccgcggg cccggatgct gaggaggcag     600
gcgacgagac acccgacgtg gaccccgagc tgttgaggta cttgctggga cggattcttg     660
cgggaagcgc ggactccgag gggtggcag ccccgcgccg cctccgccgt gccgccgacc      720
acgatgtggg ctctgagctg cccccgagg gcgtgctggg ggcgctgctg cgtgtgaaac      780
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gcctagagac cccggcgccc caggtgcctg cacgccgcct cttgccaccc tgagcactgc 840
ccggatcccg tgcaccctgg gacccagaag tgcccccgcc atcccgccac caggactgct 900
ccccgccagc acgtccagag caacttaccc cggccagcca gccctctcac ccgaggatcc 960
ctaccccctg gccccacaat aaacatgatc tgaagcagca aaaaaaaaaa aaaaaaaaaa 1020
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1050

<210> 243
<211> 647
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (525)..(525)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (578)..(578)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (581)..(581)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (620)..(620)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (629)..(630)
<223> n equals a,t,g, or c

<400> 243
gtgaaacgcc tgggctcaag ctgattcacc tgcctccacc tcccacagtg ctgggattac 60
aaacatgatc ccccacgccc agccaacaca aaacttctga tgctctgttt tctcatctgt 120
gaactggagc taaggctaag tggtctgtct gtttaataag agtttgaatc agatggcctg 180
gcatgaagag tcactggcct gagagaatgt caggggcatt tgtaaatgtg taaagggctg 240
aaaaatcctg aggattatt attattgcta ttgttgttat tattcacaga cacatycaac 300
agccattgtc tgcctcctta tctgtcatgc tttctgcacg agcgtcagcc tgagcttcaa 360
tctgtgtgta tatctgcagc ttacgtcctt gcacccctcc agaacccagt ttcatccttg 420
taggtttttc craagcagga tttgcacaag tggcgtgttt tcttaagtat ttattttgca 480
ggccatttac tcggcatggc tatttttaca gtgggtaagg agcanggcta aaaataactt 540
agctcataac cagacaggtt ctgcatttga cattacgngg nattcatttg catcccattt 600
ggtcgccttt ctggttaacn ggtagaatnn aagaaagctc acccgaa 647

<210> 244
<211> 1321
<212> DNA
<213> Homo sapiens

<400> 244
gcggggggga ggaggagggg gaggagggag cggagatctc ggggctcgga gccggccgcc 60
gctccgctcc gatcgctgtg ggcttggtt ttttgggggt gggggggcgg gggggctcag 120
atatggaggc aaatgggagc caaggcacct cgggcagcgc caacgactcc cagcacgacc 180
ccggtaaaat gtttatcggt ggactgagct ggcagacctc accagatagc cttagagact 240
attttagcaa atttggagaa attagagaat gtatggtcat gagagatccc actacgaaac 300
gctccagagg cttcggtttc gtcacgttcg cagacccagc aagtgtagat aaagtattag 360

```
gtcagcccca ccatgagtta gattccaaga cgattgaccc caaagttgca tttcctcgtc    420
gagcgcaacc caagatggtc acaagaacaa agaaaatatt tgtaggcggg ttatctgcga    480
acacagtagt ggaagatgta aagcaatatt tcgagyagtt tkgcaaggtg gaagatgcaa    540
tgctgatgtt tgataaaact accaacaggc acagagggtt tggctttgtc acttttgaga    600
atgaagatgt tgtggagaaa gtctgtgaga ttcatttcca tgaaatcaat aataaaatgg    660
tagaatgtaa gaaagctcag ccgaaagaag tcatgttccc acctgggaca agaggccggg    720
cccggggact gccttacacc atggacgcgt tcatgcttgg catggggatg ctgggtgagt    780
ctggacagga ccgcaggtca ccatggactg ggagggctat ggaggcctct actcccaact    840
gggtcaccta ccagtggggc aaactgcttc acctttctaa gcctcagttt ccttgtctgt    900
agatgaggat gataattccc cgttccaaga cagttgtgat gattaagtgt gggtgtgtgt    960
gtgtgcatgc atgtgtgtgt gtgtgtgtgt gtgtttgtat ttataatatt gccccatgcc   1020
tggcttatag gatatgttag actattttct ctcttttcca tctccttcct caaaagaagg   1080
aaaagtcccc ctctatctgc ctcagccctc tcatctgagt gggagttytt aagatgtaag   1140
gactcctggc tgacttgact tgtgtgggct aaggctacgt tttctaaaac ttgggagagg   1200
agggaagtgg taagggtggg cgataatcct gtctatttaa atgattaaca tttttctctt   1260
gggatatcaa aatttgcatt taaatggatg ttttaaatag cctgttttac tctttatttg   1320
c                                                                   1321
```

<210> 245
<211> 1084
<212> DNA
<213> Homo sapiens

<400> 245

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ggatggcgct acgtctgctg cggagggcgg cgcgcggagc tgcggcggcg gcgctgctga     60
ggctgaaagc gtctctagca gctgatatcc ccagacttgg atatagttcc tcatcccatc    120
acaagtacat cccccggagg gcagtgcttt atgtacctgg aaatgatgaa aagaaaataa    180
agaagattcc atccctgaat gtagattgtg cagtgctcga ctgtgaggat ggagtggctg    240
caaacaaaaa gaatgaagct cgactgagaa ttgtaaaaac tcttgaagac attgatctgg    300
gccctactga aaaatgtgtg agagtcaact cagtttccag tggtctggcg gaagaagacc    360
tagagaccct tttgcaatcc cgggtccttc cttccagcct gatgctacca aaggtggaaa    420
gtcctgaaga aatccagtgg gcagtgtgtg aagaaacccct gaaggtcggg cctcaagtag    480
gtctctttct agatgcagtc cgtttttgga ggaraagact ttcgagccac ataggtgcam    540
caagtartaa agaaaccctg gatawtctct acgcccggca aaagattgtt gtcatagcga    600
aagcctttgg tctccaagcc gtaratctgg kgkacattga ctttcgagat ggarctkggc    660
tgcttagaca gtcacgagaa ggagccgcca tgggcttcac tggtaagcag gtgattcacc    720
ctaaccaaat tgccgtggtc caggagcagt tttctccttc ccctgaaaaa attaagtggg    780
ctgaagaact gattgctgcc tttaaagaac atcaacaatt aggaaagggg gcctttactt    840
tccaagggag tatgatcgac atgccattac tgaagcaggc ccagaacact gttacgcttg    900
ccacctccat caaggaaaaa tgatctgtta aatgaagctg tcatcaggct aaagggtatt    960
gaagctgcag agggatcaac ttgtgcttgc cagaggacgc caatgaagtt tgaaacacca   1020
acaatcagag attttgtttc tgttcctcat taaatcatga gcttttgtgc cgagaaaaaa   1080
aaaa                                                                1084
```

<210> 246
<211> 1776
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1748)..(1748)
<223> n equals a,t,g, or c

<400> 246

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agccactgtg cccagcctcg gctcaggttt ttmaatacag tcttgacctt ggcattcagt     60
atcctcacag catggttcta attaactttc tagctctatt tccctttcc tgctccctct    120
ctctacaact agtctttctc tgattgcccc gccctcaacc catctaaact agaccccagg    180
gaagcacctt ggtccccttc ctctctccca ctcaccatcc aaccaatcac cagagcctgt    240
acattctata ttttcaacat cgattcaatt gtctacttct ttctagcctg ccctctctga    300
ctgggactcc ttgagccagc ctgatcaccc caatccatcc ctcacactgt gcccatcttt    360
```

ctgaagtagg aatctgatca caccamcctg ctaaaaacac tctggttctc cccacggcat 420
gtggtgccct tgtatagctg gcaaagcctt gcatggcacg gccccagcct gtgcttcaac 480
tcaattgccc gactctctcc agctctgctg agccacctaa gtcacagatg gtttctcctc 540
tcatctctgc tctcttccat gtgccatttc tgtggcttgg aatgttcttc cctcattctc 600
tttctggccc tttcccgtca caccttagac gtgcatcttc ctctcgaaaa cctctagtga 660
agcctcccag ggccaggcag taccctcctc tggcttcttc tggatacaga ggaagaatct 720
gagcatcgat tctccatctc agcaggcctc tgtgtgcctg ctgactccga ctagaccaga 780
gatccgtaag gacagggatc gagttttttt tcttttaatk cactgcctca aaaatcctct 840
gtgcattacc tattcatcct cttctctccc ttaacctgaa ccagtgatct tactgtctcc 900
atcattgttt ttttcttttc ttttcttttc ttttttttt ttgaggtgga gtctggctct 960
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tcaagcgatt ctcctgcctc agcctcccca gtagctggga ttacaggcat gcgctaccat 1080
ccccaactaa tttttgcctc cataattytg ccttttstag aatgtcatac aggtggaatt 1140
actcagtatg ctgccttttt cagattggct tctttcactt agtaatatgs tygtttttg 1200
agacagggtc ttgctctgtc gcccaggcta gagtgtggtg gtgcgatctt agctcactga 1260
aacctccacc tcccaggttc aagtgaytct sctgcctcag cctcccgagt agctgggact 1320
acaggcacgt gccaccatac ccggctaatt tgtggatttt tagtacagac ggsgtttcgt 1380
catgttggcc agtgtgytgt tgaattcctg acctcaagtg atccacctgc ctcagcctcc 1440
caaagtgttg cgattacagg tgtgagccac tgcgccaagc ctcatttagt aataygcatt 1500
taaactttct ccatgkcttt aatggcttga tagctcattt atttttatca wggaatattt 1560
cattgtctgg atggaccaca gtttatttct ccattcacct actgaaggac atctcggttg 1620
cttctaagtt ttggcaatta tgaataaagc tgctataacc atcaagtgca ggtttttgtg 1680
tggacctatt atcaactaat tcgggtaaat ctcaaggagt gcaattgctg gatccacagt 1740
aagagtgngt ttagttttaa gtgcttggcc attttc 1776

<210> 247
<211> 784
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (6)..(6)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (32)..(32)
<223> n equals a,t,g, or c

<400> 247
ngagtntaat tgctggatca cacagtaaga gngtggttag ttttaagtgg ctgtgccatt 60
ttgcattccc accagcaatg aatgagagtt tctgttgctc cacattctca ctaccattcg 120
gtgttgtcag tgttttgcat tttggccatt ctagtaggtg tttacatggt atctagtcat 180
ttgaatgggc atatgatgtg gaacatcttt tttttttat tttwttatta ttatacttta 240
agttttaggg tacatgtgca caaygtgcag gttwgttaca tatgtataca tgtgccatgy 300
tggtgtgctg cacccaytaa ctcgtcatyt agcattaggt atatctccya atgctattgg 360
aacatctttt catgtgttta tttgccatct gtatatcttc cctgatgagt tggggatgca 420
ttctttccat ctcagagtcc ccagaaacta acatagcagt tggtacagag ttggtgctca 480
acaaacatca gcttaggaac tatgtcctat gttttttgt ttttttttt ttttaaaaag 540
gaatgtgagc tgttcccaaa acgtatgtcc ttccccatg cctctaccct gcccttccac 600
aaactttctg atcttcagca cacactaccc aaccatcaag gctgagactt cccgtggcca 660
gcagtgtctc atgctggctt caagccccac agcactgctt ttttcaactt ctcttgtggt 720
ttagactgtc tttagcccag caagagaatt cgatatcaag cttatcgata ccgtcgacct 780
cgag 784

<210> 248
<211> 699
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (12)..(12)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (30)..(30)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (46)..(46)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (66)..(66)
<223> n equals a,t,g, or c

<400> 248
ggttcatgct tnaaccccat ttgctggatn ctgctttgac cctgtntccc tgtactggtg 60
ttatgngaat cctggcacac attgctatcc cactctgaga ggmcwtgagc aaagaamccc 120
cagtrgcaga agccacattg tgctcaggtc ttagttctaa caaacaccat tccccattaa 180
aaggaaccag gctccttaga gaaatggatg attccagggc tgtggcaggg taggtacaag 240
atgaacctaa agtgtcgttt tataccagaa agtaagaaag tattaaagtg tttaaaaaag 300
tgatgggagc atatcacaag gattcagaag ggataccaac tggctaaatc tggaacaatt 360
tgatcaccaa agtaagtaca ataataaatt ctaagctatt gaagtaaagg catttattat 420
gtgtagtaat aataaataga taatgagaga gaaatgagga ctcatgctta cagtaaaatg 480
ccaggagctg actggcataa atgtggaagg aaggctggag tgggaaaatt attattttgc 540
aaccatcatg gtaattacca gatcagataa ggatcaacag atgccaaatc tagggcaaat 600
ttgatgagga gcagaatatt tgcactgtct ttgagagttt ctcccagaga tcacttattt 660
gttgtaaaaa aaaagaaaaa aaaaaaaaaa aaactcgag 699

<210> 249
<211> 774
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (618)..(618)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (715)..(715)
<223> n equals a,t,g, or c

<400> 249
gtctacctcc gggctgaaac gtcaccatgc ctccccacag acagacggat ggacagatgg 60
gcctccctgc acctgctctg tgggtgtggg ggctcctgct cagcagcagt ttccagaccc 120
ttctccctgc tttccccaag ccacccgcct tgaatctggg gtgctctacc agacccatcc 180
cctcatttct aaagatttga gccactagtc gtgtccctct ccctcagaaa tgccttggtg 240
acacttggct gctttcaact cttccaccca tctgcctctt ggtctcatct ttaccttctg 300
ctaaaggtcc tgacccccac ccccgccacg ccatggggca ccccatggtg gtgcgtcctt 360

```
gggagcagct ctgtcccttt ccccgtggcc tttgccccgc ctcctatgac ttcgattccc     420
acctgtcccc gacccctggg accactgacc gggcccgatc accctgtcac tgccctgtca     480
tctgcttacc ccacacggtg ctctgctgac ccaggtcttg ctgtctccca ayagccccac     540
gaggcttycc gtcgctcctg gacactrmag gctgagcccg ctgccccgcc gcctccatga     600
ggaaggcttt tcctctgnga gccccaggcc acccttttccc tcctttaagt aattacttaa    660
gtcccttgcc agggccctcc cagtaccctt tctaaagaca cccctgcccc agcangctgc     720
aggctcctgc tccactttcc tctcaggccc tcgtcgctgt ggtgctgcct ttga           774
```

<210> 250
<211> 1396
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1187)..(1187)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1325)..(1325)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1327)..(1327)
<223> n equals a,t,g, or c

<400> 250

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cctcgagcca tgtgtccagg tggggcagat catggagggc gcccaggtgc ggtgctgagg      60
ctgagcatgc actggctggg gagggtgggc agagcaggag gaaatccctt gttctccgga     120
gctggagagc cagaaagagc cctgcagcct gggcctcatc atcacacctc gccctcaagg     180
cctccaggca cagcatccac tgccagcctc tgctcctgcc tctgagggtc tgtctccaag     240
gtcttttggg ggctgcccca gctccccccaa cacagacagc accagagctg ggcccacctg    300
tgaggtgctg agttccccat ctcagagact gtgcgagcag aggcagggag gcgcttgatg     360
tcggatggag aaaggacagg ggaggggtgt ggggctcagg gccccgccag gtgaaggaac     420
aagcttggaa gggtgtcctt atgtctgaga gttggggaga caccccccaag ccccagatgg    480
rcctcgaatg ccaggcaggg ccaagctggg cccagaagtg ggawggwtcc cttggctgcc     540
ccaggaatgc aggttccggg gcaagaatcc agccctggct ggttgaagtc catcccaagt     600
ctccctcccc acgaggctcc tgcagatgcc aggaatgggg ctggattcca gattccaagc     660
ctggcsgccc agcccctatc tgggacccca gcccagagcc cccaggcctg gcctccaacc     720
tggccccagc ctcaggggag ctgaattcag agaatcctgt cctaggagcc agaagcgggg     780
gagggaggra gggcggccct gtcctgggtg caggcccggg ggctgggggy tgcccgcccg     840
tctgggtcag ccgcagctgc aaaccggccc tggctgagtc atggsgcctc catctccagg     900
gcctggcttg aggtggggaa tagcagtgag gttggacatc caggcacctg agggtgggca     960
gggctccctg cggctggggt ggccagtggc acctggctgt tgccccccctg caccccagcc   1020
ctttggcccc caagtctctg ccacctccct ggggttctgc tcccatattc ctcacaccca    1080
gcacagaacc cagcatgtct cctgtagaca cctgcatata aaccctgact cacacacaca    1140
cacacacaca cacacacgca cacatgcagg ccaggctcct cggccangtc accctaccgg    1200
cagagctcta gacatttctg gcctctggtg actattcttc aggcagctca ccctgcaagt    1260
ctttattgag cacctactgt gtgccaggca gtggtacagc aagggcagaa gccccacctc    1320
caagnanctg aacccctgcc gtggcagaga cagaaaacaa aggcagcacc acggcgacga    1380
gggctaaaga gaacgc                                                    1396
```

<210> 251
<211> 1397
<212> DNA
<213> Homo sapiens

<400> 251

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tcgacccacg cgtccgctga attgcggccg tatgcgcggc tctgtggagt gcacctgggg      60
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ttgggggcac tgtgccccca gccccctgct cctttggact ctacttctgt ttgcagcccc 120
atttggcctg ctgggggaga agacccgcca gctgcttgag tttgacagca ccaacgtgtc 180
cgatacggca gcaaagcctt tgggaagacc atatcctcca tactccttgg ccgatttctc 240
ttggaacaac atcactgatt cattggatcc tgccaccctg agtgccacat ttcaaggcca 300
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cttttccagg tccagccgac cagcccaacc ccctcgcctc ctgcacacag cagacacctg 420
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<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

<400> 254

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<211> 2409

<212> DNA
<213> Homo sapiens

<400> 255
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<211> 876
<212> DNA
<213> Homo sapiens

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cggcagatac acgggtggca gtggtgaact atgctagcac cgtgaagatt garttccawc 480
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<211> 1586
<212> DNA
<213> Homo sapiens

<400> 257
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<210> 258
<211> 1011
<212> DNA
<213> Homo sapiens

<220>
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<222> (2)..(2)
<223> n equals a,t,g, or c

<400> 258
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<210> 259
<211> 1395
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1382)..(1384)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1390)..(1390)
<223> n equals a,t,g, or c

<400> 259
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<210> 260
<211> 270
<212> DNA
<213> Homo sapiens

<220>
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<221> misc_feature
<222> (260)..(260)
<223> n equals a,t,g, or c

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tgtgatccgc aaggcccaaa cgatgtgact gccaagctcc tctgtccctg atttggtgtt 180
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cgttgctggg attcggtggn ggggartcgg 270

<210> 261
<211> 2324
<212> DNA
<213> Homo sapiens

<220>
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<222> (15)..(15)
<223> n equals a,t,g, or c

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<220>
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<223> n equals a,t,g, or c

<220>
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<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (107)..(107)
<223> n equals a,t,g, or c

<400> 261
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gctttatttg tgaaatttgt gatgctattg ctttatttgt aaccmttata agctgcaata 180
accaagttac camcamcaat tgcattcatt ttatgtttca ggttcagggg raggtgtggr 240
aggtttttta aagcaagtaa amcctctaca aatgtggtat gsctgattat gatcatgamc 300
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cctttttttt tttttttcat cttttattta tttattattt ttttttacta aggcacatga 720
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<210> 262
<211> 585
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (570)..(570)
<223> n equals a,t,g, or c

<400> 262
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tggtggctat gatagtttcc ggagttataa cagcagtgtg ggcagtgaga gcagctccta 180
tctggaggag tcaagtgaag cagaaaatga ggatcgggaa gcaggggaac tgccgacctc 240
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tggtctkcca aaattggagc cttcctccaa tctcaaagga caggacagct ggcaratkgg 540
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<210> 263
<211> 4344
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (754)..(754)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2242)..(2242)

<223> n equals a,t,g, or c

<400> 263
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ccagagacca agatcatcaa gacagatggc aaagggtggg gcctggtcgc caagagggac 180
atcagaaagg gagaatttgt taacgagtac gttggggagc tgatcgacga ggaggagtgc 240
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tcttaaaaaa aaaaaaaaaa aaaa 4344

<210> 264
<211> 1258
<212> DNA
<213> Homo sapiens

<400> 264
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tataccttgc cctctatcat tataaatggt tgccatggtg tttctaaaaa taagtgtttt 180
accattaatg tgtagagggc aaacaaagca taaagtacta agggatcatg cttatcctag 240
ggtctcacag aagagaggac atatttaatt aatcttgtga attacagaac aggttgtggt 300
ccagacacca agaatcatag gggttttttt ttaaaaaacc taatagaagt agggtgacct 360
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ctggctttac ctctggttaa tgcttgtgtt aataggaagg aaaaatcact ttatcttttc 480
ttccaagccc ctccctgcct gacttaccca gactgggatt accagatacc aggtgattta 540
tgtggagatg atttttcacc tttaaactct aagccaagtg taagaaactc ttgatagcta 600
tgtctatttt atatcagtca ctgagacttt tttttaagtt tttatttatt attaagacaa 660
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taaacagaaa tggagacctg aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 1258

<210> 265
<211> 1739
<212> DNA
<213> Homo sapiens

<400> 265
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tccagaatgg tgtttctgaa gttcttctgc atgagtttct tctgccacct gtgtcaaggc 180
tacttcgatg gccccctcta cccagagatg tccaatggga ctctgcacca ctacttcgtg 240
cccgatgggg actatgagga gaacgatgac cccgagaagt gccagctgct cttcagggtg 300
agtgaccaca ggcgctgctc ccagggggag gggagccagg ttggcagcct gctgagcctc 360
accctgcggg aggagttcac cgtgctgggc caccaggtgg aaggatgctg ggcgcgtgct 420
ggagggcatc agcaaaagca tctcctacga cctagacggg gaagagagct atggcaagta 480
cctgcggcgg gagtcccacc agatcggggg atgcctactc caactcggac aaatccctca 540
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tcaacgagga ctttctggga atgctggtcc acaccaggtc cctgctgaag gagacactgg 660

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ttagaaagag ggaatcaaat cagccccgtt ttggaaggtg gggacagaa aatggggcta      840
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gcacagttta tgtggtgcgg aattaaactt ccccatcctg cagattatgt ggaaataccc    1140
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<210> 266
<211> 538
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (462)..(462)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (498)..(498)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (520)..(520)
<223> n equals a,t,g, or c

<400> 266

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gatgttatat caaaatatgt tgttatactt taggataatc ggtgtgttag ccctgaattt     180
cagcataagt cccatttttt tccatgggag tctaggaaag ctatatgttt attcagcagc     240
aaaatacagt ttggaactta aataaactat tgatcaattc tggtcttatg ctagaaggaa     300
taaagcatca agaaaaagaa aagattgctg tcaagaccag gaaaattgac aatagagtat     360
tagaatgcag aaatgagggg aagtggaaar gccascaagt aggagagaaa aagtgcaggg     420
acagtagaaa gtgaatgtag gagcttctga cccagcactc angaacgcaa ttcatcccta     480
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<210> 267
<211> 1346
<212> DNA
<213> Homo sapiens

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<220>

<221> misc_feature
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<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (150)..(150)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (323)..(323)
<223> n equals a,t,g, or c

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<222> (1307)..(1307)
<223> n equals a,t,g, or c

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<221> misc_feature
<222> (1337)..(1337)
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<222> (1341)..(1341)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1343)..(1343)
<223> n equals a,t,g, or c

<400> 267
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<212> DNA
<213> Homo sapiens

<220>
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<222> (36)..(36)

<223> n equals a,t,g, or c

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<222> (93)..(93)
<223> n equals a,t,g, or c

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<222> (158)..(158)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (592)..(592)
<223> n equals a,t,g, or c

<400> 268
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<211> 1177
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<213> Homo sapiens

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<223> n equals a,t,g, or c

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<221> misc_feature
<222> (1115)..(1115)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1142)..(1142)
<223> n equals a,t,g, or c

<220>
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<223> n equals a,t,g, or c

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ctgctgcagg agttcgagga gaagagtggc cgcacctttc tgcacaccgt ctgcttctac 660
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<210> 270
<211> 1775
<212> DNA
<213> Homo sapiens

<220>
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<222> (820)..(820)
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<400> 270
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<210> 271
<211> 866
<212> DNA
<213> Homo sapiens

<220>
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<222> (14)..(14)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (27)..(27)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (33)..(33)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (105)..(105)
<223> n equals a,t,g, or c

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<210> 272
<211> 1237
<212> DNA
<213> Homo sapiens

<400> 272
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<210> 273
<211> 1681
<212> DNA
<213> Homo sapiens

<400> 273
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<210> 274
<211> 1863
<212> DNA
<213> Homo sapiens

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<211> 1134
<212> DNA
<213> Homo sapiens

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<210> 276
<211> 626
<212> DNA
<213> Homo sapiens

<400> 276
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<210> 277
<211> 152
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (41)..(41)
<223> n equals a,t,g, or c

<400> 277
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gggatccact agttctagag cggccgccac cgcggtrgag ctccagcttt tgttcccttt 120
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<210> 278
<211> 1760
<212> DNA
<213> Homo sapiens

<220>
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<222> (1693)..(1693)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1748)..(1748)
<223> n equals a,t,g, or c

<400> 278

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<210> 279
<211> 880
<212> DNA
<213> Homo sapiens

<400> 279

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<223> n equals a,t,g, or c

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<221> misc_feature
<222> (1037)..(1037)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1058)..(1058)
<223> n equals a,t,g, or c

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<211> 646
<212> DNA
<213> Homo sapiens

<220>
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<222> (19)..(19)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (544)..(544)
<223> n equals a,t,g, or c

<400> 281
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<210> 282
<211> 1590
<212> DNA
<213> Homo sapiens

<400> 282
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<211> 1179
<212> DNA
<213> Homo sapiens

<400> 283
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<210> 284
<211> 819
<212> DNA
<213> Homo sapiens

<400> 284
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<210> 285
<211> 1792
<212> DNA
<213> Homo sapiens

<400> 285
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<210> 286
<211> 1673
<212> DNA
<213> Homo sapiens

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<210> 287
<211> 2084
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (775)..(775)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2080)..(2080)
<223> n equals a,t,g, or c

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gtccaggact tgacatctta agatgcgtct tgtccccttg ggccagtcat ttcccctctc    1500
tgagcctcgg tgtcttcaac ctgtgaaatg ggatcataat cactgcctta cctccctcac    1560
ggttgttgtg aggactgagt gtgtggaagt ttttcataaa ctttggatgc tagtgtactt    1620
agggggtgtg ccaggtgtct ttcatggggc cttccagacc cactccccac ccttctcccc    1680
ttcctttgcc cggggacgcc gaactctctc aatggtatca acaggctcct tcgccctctg    1740
gctcctggtc atgttccatt attggggagc cccagcagaa gaatggagag gaggaggagg    1800
ctgagtttgg ggtattgaat cccccggctc ccaccctgca gcatcaaggt tgctatggac    1860
tctcctgccg ggcaactctt gcgtaatcat gactatctct aggattctgg caccacttcc    1920
ttccctggcc ccttaagcct agctgtgtat cggcaccccc accccactag agtactccct    1980
ctcacttgcg gtttccttat actccacccc tttctcaacg gtcctttttt aaagcacatc    2040
tcagattaaa aaaaaaaaaa aaaaaaaaaa aggggggggcn gcnt                    2084
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<210> 288
<211> 720
<212> DNA
<213> Homo sapiens

<400> 288

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ggcacgagat ttctcacaat gacaaattct caaatattgc taatagtact gtggattttc      60
ctacattggt aaattgaagg aattgctaaa tgctgaattc agcaaccagt ttgagattgt     120
tgaaaataaa gattgtttct ttttcaatgc aagttcacag atcactggag ttctagctac     180
agtttgttct agaccagagg ttgcagatat ttttgtccta taaagagaca catggttaat     240
atttttggct ttgtgagttg tatagttttc gttgtagctg ttcagctctg ctacatgaag     300
caaccataga ccataccttta acaagtggtc acttttgagt accaataaaa ctttatttag   360
aaataacaga gggctggatt tggtcctagt ttgctgaacc cttttctaga tgaaggctcc     420
tcttgccaag actggctccc taccttggct gacaaattct cactttggga cttagtcatt     480
gttgctgctc tctgttattt tgcatgtctt ttctcatgtt taggtgctgt gtcttaatac     540
ttttttctta catttaattt aacaatcatt actgagcgct ggtatgtcta gtttcttttc     600
tcttctttcc tcctttttctt ttctttttttt cttttctttt atttgaaggc tctcactctg  660
tcactccagc ctgggtggca gaccaggacc ctgtctctaa aaaaaaaaaa aaaaaaaaaa     720
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<210> 289
<211> 738
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (646)..(646)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (670)..(670)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (696)..(696)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (707)..(707)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (718)..(718)
<223> n equals a,t,g, or c

<400> 289
catcagacca cacccagcag tcagaaaaga ggtgcagggg cccgggctgg gacagtgaag 60
agtgctgggc agtctgtggt cctctgtatc tcaacttttt catcttaaaa aaacaaatag 120
ggttgtgtgt gtggctggtg gtcataaggt cctttctggc tctaataacc tgagcttctg 180
ttatgaagct gggaccctta gagcctcagg atgatcctct gtttgtttgt gaagccccaa 240
tcaggtgcta agcaccatag tggcacttag ctgaagctcc tctgtaactc ctgtgggccc 300
tgccttgccc accccсgaca gctgctgcag tgctcctgag cagcacaggc ctgatggagc 360
ttctggagaa gatgctggcc ctcaccttgg caaaggcaga ttctcccagg actgcactcc 420
tctgctctgc ctggctgctc actgcctcct tctctgccca gcagcacaag ggcagtttgc 480
aggttcacca gacactctct gtggaaatgg accargtatt gaaggctctc agctttccaa 540
agaaaaaggc tgcactactc tcaactgcca tcttatgctt cctgcggaca gccctgcgac 600
aaagcttttc ctctgcctgg aaccctggtg cccttaaggg cccagncact gcagccacca 660
aggacactgn cctaacttca ctgcgaatgt ccaagnccgg ccctggncat tgggctgnaa 720
aaacctcctg gtgcaaaa 738

<210> 290
<211> 935
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (6)..(6)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (14)..(14)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (16)..(16)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (50)..(50)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (95)..(95)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (101)..(101)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (139)..(139)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (176)..(176)
<223> n equals a,t,g, or c

<400> 290
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aagcttttc ccaaaaggaa aaaaagggtt gccantaatt nttcaaggat tgcccatctt 120
taatgctttc cttggggana agccttgcga caaaagcttt ttccttctgc cctggnagcc 180
ctggtgcctt caggggccca gccactgcca gccaccaagg acactgtcct agctccactg 240
cgaatgtcgc aagtccggtc cctggtcatt gggctgcaga acctcctggt gcagaaggac 300
cctctattgt cccaggcctg tgttggctgc ctggaggcct tgcttgacta cctggatgcc 360
cggagcccag acattgctct ccacgtggcc tcccagcctt ggaatcggtt tttgctgttt 420
accctcttgg atgctggaga gaattccttc ctcagacctg agattttgag gctcatgacc 480
ctgtttatgc ggtaccggag tagcagtgtc ctctctcatg aagaggtggg tgatgttctg 540
caaggtgtgg ctttggctga cctgtctacc ctctcgaaca ccacactcca ggccctgcat 600
ggcttcttcc agcagctcca gagcatggga cacctggctg accacagcat ggcccagacc 660
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gacatgctct gcctgggagg ggtggctgta tccctgtccc acatcagaaa ctgatcctca 780
ggacttgaag gcccagaagt ggagagagaa tgagacctgg agacaaaggg cataattgtt 840
ggggaaatgg atgacagctg aagctattca tatggagcca tatactctat tgttgaaata 900
gaataaggaa ataaaatgat acactcacaa aaaaa 935

<210> 291
<211> 871
<212> DNA
<213> Homo sapiens

<400> 291
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aagggaagaa ctgcctccgc tgctggccag aactgtctgc cttgatagac tatgacctgc 120
agatcctctg ggtgacccca gggccaccca cagaactttc tcaaagtatt cactccttgt 180
tcctagagga taataatttt ctcaaaccct ggtaccttga tcgtgaccat ttggaagaag 240
aaacagccaa attcttcact caagtacacc aagccattaa aacgttacga gatgataaaa 300
cagtacttct ggaagagatc tacacgcaca agaatctctt tactgagagg ctgaataaga 360
tatctgatgg gctgaaggag aaggagcccc acccctctcc atgaatgcct tcccggctcc 420
atctcctact tgcaccccag aacccccttgg cttctgtctg cctccccagc acctcagttt 480
ctctaccttc tcaccctccc tggcagcctg caatgagtcc tgtgccagga accggcggac 540
ctccctgtgg gctgtgagtc tcagcagtgc tctactcctg gccatagctg gagatgtttc 600
ttttactggc aaaggaagaa ggaggcagta aaggaacagg gcagcccgca tgtcttccag 660
aagtgaacag aggccgcagc taccaccgtc acaaagttca ctcatctctg ggtcccggtg 720
accccatccc cccatacccct ccatcctggg tcctggggcc ccaaagctct gaggcctagg 780
agactgcgct gtctcgtggt ttgcctactc ctacaccttt gtaaagagtc tcttcattaa 840
aacccctctt cataaaaaaa aaaaaaaaaa a 871

<210> 292

<211> 881
<212> DNA
<213> Homo sapiens

<400> 292
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ccattgaagg gaagaactgc ctccgctgct ggccagaact gtctgccttg atagactatg 120
acctgcagat cctctgggtg accccagggc cacccacaga actttctcaa agtattcact 180
ccttgttcct agaggataat aattttctca aaccctggta ccttgatcgt gaccatttgg 240
aagaagaaac agccaaattc ttcactcaag tacaccaagc cattaaaacg ttacgagatg 300
ataaaacagt acttctggaa gagatctaca cgcacaagaa tctctttact gagaggctga 360
ataagatatc tgatgggctg aaggagaagg gagccccacc cytctccatg aatgccttcc 420
cggctccatc tcctacttgc accccagaac cccttggctc tgtctgcctc cccagcacct 480
cagtttctct accttctcac ctccctggca gcctgcaatg agtcctgtgc caggaaccgg 540
cggacctccc tgtgggctgt gagtctcagc agtgctctac tcctggccat agctggagat 600
gtttctttta ctggcaaagg aagaaggagg cagtaaagga acagggcagc ccgcatgtct 660
tccagaagtg aacagaggcc gcagctacca ccgtcacaaa gttcactcat ctctgggtcc 720
cggtgacccc atccccccat accctccatc ctgggtcctg gggccccaaa gctctgaggc 780
ctaggagact gcgctgtctc gtggtttgcc tactcctaca cctttgtaaa gagtctcttc 840
attaaaaccc ctcttcataa aaaaaaaaaa aaaaaactcg a 881

<210> 293
<211> 1598
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1067)..(1067)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1069)..(1069)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1577)..(1577)
<223> n equals a,t,g, or c

<400> 293
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tctgcctttr aaaatgcttc caaaagtaga ccctgtcccc acacaggtca agactacaga 180
gaaggctttg tagaaatgtg tcacctatgt acacctgcta cttacacatt tcctcttttg 240
gaaaaatgag atacttagaa taacargaaa attaagacat actggcctgg tgccagcaga 300
tggcttttct atagacaaac taggttagtg tggaagatat aggttaaaat aaactatgct 360
gttttattta tcttcccaac ctgattggca gctagacttt tttagggtct catttaatgg 420
ccctgttttt ttcattatta tatttaatga tagggcagga tttcgtatgc aagctcttgt 480
ttctcaggct gcctgcagaa gaagtcgcta taaattatct gttgtctaca tggtacaagg 540
cccattgact catctgatgc ttgttttgtt aatttcttta atatttttat cacggggcag 600
tgggagggct tgggctttta gccacagctg ttttaagact tctgatctcc tgccctgcag 660
gaataggtgg gaagtcattg aattttttaca ctatagtaat ttgcattccc acataagttt 720
gagtgttacg aaaacattcc tttaaaggga tctgtgctac acaaaatatg ccaggacctc 780
acagacaaag ccattgctag aaatgtcatt ccaatgatca gatctggaaa caggctgcca 840
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ttgaaacacc tatttctact caggtactca ttgtcctgtt actgattcac ctttctgatc 960
cttttcaacc agttttcccc caaggggggga aattttactt aacctctagt atttgaacaa 1020
ctcaatattt gaattgttgc cccatttgct tttacctgta ctgtatncnt ggtcatctca 1080
aatggcgtct aaacccagct actttgcatt ccagaagttt ccattccctc caattccacc 1140

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taatttttca tctgtcctag ttactggctc tttcttcatg tcttatttct cttgctttgg   1200
gagcttaaaa gattttacaa gacctaattt tgggttcctt ccttggagcc atagttaccc   1260
tgccaagaag agtagaaaat gggttcaact cctgtttcgc tccaccaaca cctctgtgag   1320
tctcatcatc agctgagcga tgatgcctta caggttgcat agcactggaa ctttcctaga   1380
gtaacggctc tgctgccagg gtttctctgg gctcattctt ccactgactt aattatgatc   1440
tatgcctaac agagccccag tacaactatt ttgcagaatg gctgttaccc tagaattact   1500
atagcacata ttgagatata gttgtactcc ctagtagata ggaactgacc ccaacaataa   1560
actttgataa taaaganaaa aaaaaaaaaa actcgtag                           1598

<210> 294
<211> 530
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (517)..(517)
<223> n equals a,t,g, or c

<400> 294
gcctggcaga gagactctga aatgagggat tagaggtgtt caaggagcaa gagcttcagc     60
ctgaagacaa gggagcagtc cctgaagacg cttctactga gaggtctgcc atggcctctc    120
ttggcctcca acttgtgggc tacatcctag gccttctggg gcttttgggc acactggttg    180
ccatgctgct ccccagctgg aaaacaagtt cttatgtcgg tgccagcatt gtgacagcag    240
ttggcttctc caagggcctc tggatggaat gtgccacaca cagcacaggc atcacccagt    300
gtgacatcta tagcaccctt ctgggcctgc ccgctgacat ccaggctgcc caggccatga    360
tggtgacatc cagtgcaatc tcctccctgg cctgcattat ctctgtggtg ggcatgagat    420
gcacagtctt ctgccaggaa tcccgagcca aagacagagt ggcggtagca ggtggagtct    480
ttttcatcct tggaagcctc ctgggattca ttcctgntgc ctggaatctt               530

<210> 295
<211> 1046
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (14)..(14)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (33)..(33)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (441)..(441)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (460)..(460)
<223> n equals a,t,g, or c

<400> 295
gagaagtcag cctngcagag agactctgaa atnagggatt agaggtgttc aaggagcaag     60
agcttcagcc tgcaagacaa gggagcagtc cctgaagacg cttctactca ccactggtgc    120
ctgacagcat gaaatttgag attggagagg ctctttactt gggcattatt tcttccctgt    180
tctccctgat akctggaatc atcctctgct tttcctgctc atsccagaga aatcgctcca    240
actactacga tgcctaccaa gcccaacctc ttgccacaag gagctctcca aggcctggtc    300
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aacctcccaa agtcaagagt gagttcaatt cctacagcyt gacagggtat gtgtgaagaa 360
ccaggggcca garctggggg ktggctgggt ctgtgaaaaa cagtggacag caccccgagg 420
ccacaggtga gggacattac nactggatcg tgtcagaagn tgctgctgag gatagactga 480
ctttggccat tggattgagc aaaggcagaa atgggggcta gtgtaacagc atgcaggttg 540
aattgccaag gatgctcgcc atgccagcct ttctgttttc ctcaccttgc tgstcccctg 600
ccctaagtcc ccaaccctca acttgaaacc ccattccctt aagccaggac tcagaggatc 660
cctttgccct ctggtttacc tgggactcca tccccaaacc cactaatcac atcccactga 720
ctgaccctct gtgatcaaag accctctctc tggctgaggt tggctcttag ctcattgctg 780
gggatgggaa ggagaagcag tggcttttgt gggcattgct ctaacctact tctcaagctt 840
ccctccaaag aaactgattg gccctggaac ctccatccca ctcttgttat gactccacag 900
tgtccagact aatttgtgca tgaactgaaa taaaaccatc ctacggtatc cagggaacag 960
aaagcaggat gcaggatggg aggacaggaa ggcagcctgg gacatttaaa aaaaaaaaaa 1020
aaaaaactcg agggggggcc cggtac 1046

<210> 296
<211> 819
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (786)..(786)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (819)..(819)
<223> n equals a,t,g, or c

<400> 296
aattcggcac gagctcaaag agtaagaatc caagtgtgtg acattacata gctttgcatc 60
tatggaaacc taaatcataa ttgtttccac tgcccaatta tgttcctttt cataacattt 120
actattctgg ctatatttat catagaacct aggaacctta gagttgacct gaatctaatt 180
aaatttcaga cctcctggcc aaagacccta gtggaagagc aaaactaaat caacatatta 240
ccaatctcaa gtatttctct gaggacccag accactgact ttttgttgtc attttcaggt 300
tgatcctata actgtatgtt ctacaatatc tgtgctccac cagctcagtg aggaatcaac 360
ggaatatcaa aagtaaatat tggtcaccat atacctttttg gtactagtct acgaaataat 420
tggctgagga actgtttcat attaaagaaa agctaaaagc aatgtgtgat cttagattag 480
acctatgatt ggaatgtatg tatattttat atacaaaata ttgaggaaat tgacaaaatt 540
taaatacaga atatggatta gataatagga atgtatcaag gtcaatattt aaaaagataa 600
tttcaacttt tattttattc agtgggtaca tgtgcagact ttgttttaca tagtacccaa 660
cagtttttca acgcttatcc cccaccctct agtaatctgc agwgwctatt attgycatct 720
tcgtggctat tgtacatggg atccatactt gattttgctc tcaacatgaa cattattggt 780
gtaganaaat gccactaagt tttkgtacgt tggcttttn 819

<210> 297
<211> 501
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(2)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (12)..(12)
<223> n equals a,t,g, or c

<400> 297

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tatgttttca aattgtttca aacctgacct ctttttgatt gctctacctt ccaaaagaaa 120
agaagggaac actaattttc ttycctgatt tacttcattg ttttcttctg ttagattaac 180
tttacctata aaagattgtc tcttgacttt atatatatat atatgtgtgt gtgtgtgtgt 240
gtgtgtgtgt gtgtgtgtgt gtgtgtgtat ttgaagagga catgtgcctc cataaaagga 300
aataaaatga gagaatacat tattgatttt gtgaaatcaa aatatttgaa ttatggtttc 360
tcaatattca aaaactcttg cagtttctgt acttatttct tctgatgcat agagtttcgg 420
ggactacata tgtttcacaa ccaaagatat ccacttgaaa taaaaacatt ataaagttaa 480
aaaaaaaaaa aaaaactcga g 501

<210> 298
<211> 3306
<212> DNA
<213> Homo sapiens

<400> 298
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ccagctcctc tgggtgagtc tgttccccct cagcctcact ttccttatcc tgtcaaatga 120
aggatttgga atgacttaag ttattcaagc aacaaacact tactgaattg tcttgccact 180
tccagggtga cattatggag ttctgtgatt ctgcaagagg ccagagggga caaggtcaag 240
tgggtgttca cctggcccct catcttcctc ctgtgcgtca ccattcccaa ctgcagcaag 300
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tcgctgtgtt ccccaggtag gtcttgaact cctggcctca agtgatcctc ctgccttgac 1740
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agtggcgcga tctccactca ctgcaagctc cgcctcccgg gttcatgcca ttctcctgcc 1920
tcagcctccc gagtagctgg gactacaggc gcctgccacc acacccagct aatttttgt 1980
atttttggta cagacagggt ttcaccgtgt tagccaggat ggtcttgatc tctgatctcg 2040
gatccgccac ccggcctcc aaagtgctgg attacaagcg tgagccaccg ggccccgcca 2100
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aaaaaa 3306

<210> 299
<211> 2194
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (441)..(441)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (987)..(987)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2034)..(2034)
<223> n equals a,t,g, or c

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<221> misc_feature
<222> (2041)..(2041)
<223> n equals a,t,g, or c

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<221> misc_feature
<222> (2121)..(2121)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
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<223> n equals a,t,g, or c

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<221> misc_feature
<222> (2184)..(2184)
<223> n equals a,t,g, or c

<400> 299
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atgacttaag ttattcaagc aacaaacact tactgaattg tcttgccact tccagggtga 180
cattatggag ttctgtgatt ctgcaagagg ccagagggga caaggtcaag tgggtgttca 240
cctggcccct catcttcctc ctgtgcgtca ccattcccaa ctgcagcaag ccccgctggg 300
agaagttctt catggtcacc ttcatcamcg ccacgctgtg gatcgctgtg ttctcctaca 360
tcatggtgtg gctggtgact attatcggat acacacttgg gatcccggat gtcatcatgg 420
gcattamttt cctggcagca nggacaagtg ttccagactg catggccagc ctaattgtgg 480

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cagtgaagat caacagccgg gggctggtct attccgtggt cctgttgctg ggctctgtcg     660
ctctcaccgt cctcggcatc cacctaaaca agtggcgact ggaccggaag ctgggtgtct     720
acgtgctggt tctctacgcc atcttcttgt gcttctccat aatgatagag tttaacgtct     780
ttaccttcgt caacttgccg atgtgccggg aagacgatta gcgctgagtc gcggcccctg     840
ggagctgatc tggacaccct gtgacactgg cgtcctcctc tcccctcctt cccccaccac     900
aggtctctcc tgcataggca gccactgtcc gttctttcac acactggaag gaagagccat     960
cgtggtcttt gtctggccac aggccangct gctgggcatc ctcctcctcc ttggagttcc    1020
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caaccacgga gatgtgccaa gcatctcatc tctcctgcac actttagtca gaaggacttc    1140
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caagatctca tagggcaggt gcaaaatagg aatgttgttc tcaagtgtca cctccagccc    1260
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gatcatgata cacaccaaaa aagtaatgat cgtaaagaca caaatcctct gtatgccatc    1620
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cttttttttt ttttttgaga tggagcctca ctctgttgcc caggctggag tgcagtggcg    1860
cgatctccac tcactgcaag ctccgcctcc cgggttcatg ccattctcct gcctcagcct    1920
cccgagtagc tgggactaca ggcgcctgcc accacaccca gctaattttt tgtatttttg    1980
gtacagacag ggtttcaccg tgttagccag gatggtcttg atctctgatc tcgngatccg    2040
nccaccccgg ccttccaaag tgcttggatt acaagcgtga gccacccggg ccccgccaag    2100
caagttgctt cttatgcaac natgttgggt tggggacttg gtccacgggg cccaggccca    2160
ataaaaatnc tttaatccct gcanaagagg ccag                                2194
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<210> 300
<211> 207
<212> PRT
<213> Homo sapiens

<400> 300

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Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
 1               5                  10                  15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
            20                  25                  30

Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Leu
        35                  40                  45

Pro Ala Cys Leu Asn Pro Val Leu Tyr Val Phe Phe Asn Pro Lys Phe
    50                  55                  60

Lys Glu Asp Trp Lys Leu Leu Lys Arg Arg Val Thr Lys Lys Ser Gly
65                  70                  75                  80

Ser Val Ser Val Ser Ile Ser Ser Gln Gly Gly Cys Leu Glu Gln Asp
                85                  90                  95

Phe Tyr Tyr Asp Cys Gly Met Tyr Ser His Leu Gln Gly Asn Leu Thr
            100                 105                 110

Val Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys Pro Val Ser Cys
        115                 120                 125

Lys His Leu Ile Lys Ser His Ser Cys Pro Ala Leu Ala Val Ala Ser
```

130 135 140

Cys Gln Arg Pro Glu Gly Tyr Trp Ser Asp Cys Gly Thr Gln Ser Ala
145 150 155 160

His Ser Asp Tyr Ala Asp Glu Glu Asp Ser Phe Val Ser Asp Ser Ser
165 170 175

Asp Gln Val Gln Ala Cys Gly Arg Ala Cys Phe Tyr Gln Ser Arg Gly
180 185 190

Phe Pro Leu Val Arg Tyr Ala Tyr Asn Leu Pro Arg Val Lys Asp
195 200 205

<210> 301
<211> 114
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (13)
<223> Xaa equals any amino acid

<400> 301
Met Ala Gly Pro Arg Ala Ser Thr Gly Pro Arg Pro Xaa Cys Leu Val
1 5 10 15

Leu Phe Leu Phe Asn Phe Ile Phe Cys Phe Met Ser Val Cys Pro Pro
20 25 30

Thr Pro Thr Pro Phe Ser Val Lys Trp Gly Ala Leu Gly Glu Ser Leu
35 40 45

Leu Pro Pro Ser Leu Ser Gln Asp Leu Pro Pro Arg His Gln Pro Ser
50 55 60

Leu Trp Thr Arg Gln Arg Ala Asp Arg Val Gly Arg Gly Leu Arg Val
65 70 75 80

Ala Arg Ala Ser Pro Pro Ala Asn Gly Pro Leu Leu Arg Pro Pro Val
85 90 95

Ser Pro Cys Pro Phe Leu Lys Gln Asn Ala Leu Val Cys Lys Pro Leu
100 105 110

Asp Ala

<210> 302
<211> 49
<212> PRT
<213> Homo sapiens

<400> 302
Met Arg Leu Cys Ser Phe Thr Lys Val Pro Met Asn Leu Phe Leu Asn
1 5 10 15

Val Ile Leu Leu Lys Phe Tyr Asn Phe Leu Phe Ser Leu Ile Leu Gly
20 25 30

Lys Ser Cys Leu Ala Ser Leu Gly Leu Cys Lys Asn Asn Lys Cys Leu
35 40 45

Ser

<210> 303
<211> 62
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (16)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (54)
<223> Xaa equals any amino acid

<400> 303
Met Val Thr Gly Phe Phe Phe Ile Leu Met Thr Val Leu Trp Phe Xaa
1 5 10 15

Arg Glu Pro Gly Phe Val Pro Gly Trp Asp Ser Phe Phe Glu Lys Lys
20 25 30

Gly Tyr Arg Thr Asp Ala Thr Val Ser Val Phe Leu Gly Phe Leu Leu
35 40 45

Phe Leu Ile Pro Ala Xaa Glu Ala Leu Leu Trp Glu Lys Glu
50 55 60

<210> 304
<211> 122
<212> PRT
<213> Homo sapiens

<400> 304
Met Cys Tyr Leu Leu Leu Leu Leu Ile Gln Thr Ala Glu Leu Leu Ile
1 5 10 15

His Pro Gln Gly Leu Gln Ala Val Ser Asn Gly Glu Ser Ala Leu Lys
20 25 30

Gly Thr Arg Pro Thr Phe Ser Ser Pro Phe Ile Leu Val Thr Glu Gly
35 40 45

Arg Lys Glu Trp Glu Gly Val Phe Leu Ser Ser Gly Trp Lys Gly Asn
50 55 60

Thr Leu Ser Asn Tyr Tyr Ile Ser Leu Val Phe Tyr Tyr Ser Arg Ile

65 70 75 80

Leu Gln Pro Tyr Phe Tyr Cys Leu Trp Gly Lys Leu Glu Met Val Thr
85 90 95

Leu Ile Arg Ser Val Trp Arg Gly Ile Asn Gly Gly Asp Lys Ile Gln
100 105 110

Leu Val Leu Glu Asn Val Lys Val Leu Lys
115 120

<210> 305
<211> 563
<212> PRT
<213> Homo sapiens

<400> 305
Met Trp Ala Val Leu Arg Leu Ala Leu Arg Pro Cys Ala Arg Ala Ser
1 5 10 15

Pro Ala Gly Pro Arg Ala Tyr His Gly Asp Ser Val Ala Ser Leu Gly
20 25 30

Thr Gln Pro Asp Leu Gly Ser Ala Leu Tyr Gln Glu Asn Tyr Lys Gln
35 40 45

Met Lys Ala Leu Val Asn Gln Leu His Glu Arg Val Glu His Ile Lys
50 55 60

Leu Gly Gly Gly Glu Lys Ala Arg Ala Leu His Ile Ser Arg Gly Lys
65 70 75 80

Leu Leu Pro Arg Glu Arg Ile Asp Asn Leu Ile Asp Pro Gly Ser Pro
85 90 95

Phe Leu Glu Leu Ser Gln Phe Ala Gly Tyr Gln Leu Tyr Asp Asn Glu
100 105 110

Glu Val Pro Gly Gly Gly Ile Ile Thr Gly Ile Gly Arg Val Ser Gly
115 120 125

Val Glu Cys Met Ile Ile Ala Asn Asp Ala Thr Val Lys Gly Gly Ala
130 135 140

Tyr Tyr Pro Val Thr Val Lys Lys Gln Leu Arg Ala Gln Glu Ile Ala
145 150 155 160

Met Gln Asn Arg Leu Pro Cys Ile Tyr Leu Val Asp Ser Gly Gly Ala
165 170 175

Tyr Leu Pro Arg Gln Ala Asp Val Phe Pro Asp Arg Asp His Phe Gly
180 185 190

Arg Thr Phe Tyr Asn Gln Ala Ile Met Ser Ser Lys Asn Ile Ala Gln
195 200 205

Ile Ala Val Val Met Gly Ser Cys Thr Ala Gly Gly Ala Tyr Val Pro
210 215 220

Ala Met Ala Asp Glu Asn Ile Ile Val Arg Lys Gln Gly Thr Ile Phe
225 230 235 240

Leu Ala Gly Pro Pro Leu Val Lys Ala Ala Thr Gly Glu Glu Val Ser
245 250 255

Ala Glu Asp Leu Gly Gly Ala Asp Leu His Cys Arg Lys Ser Gly Val
260 265 270

Ser Asp His Trp Ala Leu Asp Asp His His Ala Leu His Leu Thr Arg
275 280 285

Lys Val Val Arg Asn Leu Asn Tyr Gln Lys Lys Leu Asp Val Thr Ile
290 295 300

Glu Pro Ser Glu Glu Pro Leu Phe Pro Ala Asp Glu Leu Tyr Gly Ile
305 310 315 320

Val Gly Ala Asn Leu Lys Arg Ser Phe Asp Val Arg Glu Val Ile Ala
325 330 335

Arg Ile Val Asp Gly Ser Arg Phe Thr Glu Phe Lys Ala Phe Tyr Gly
340 345 350

Asp Thr Leu Val Thr Gly Phe Ala Arg Ile Phe Gly Tyr Pro Val Gly
355 360 365

Ile Val Gly Asn Asn Gly Val Leu Phe Ser Glu Ser Ala Lys Lys Gly
370 375 380

Thr His Phe Val Gln Leu Cys Cys Gln Arg Asn Ile Pro Leu Leu Phe
385 390 395 400

Leu Gln Asn Ile Thr Gly Phe Met Val Gly Arg Glu Tyr Glu Ala Glu
405 410 415

Gly Ile Ala Lys Asp Gly Ala Lys Met Val Ala Ala Val Ala Cys Ala
420 425 430

Gln Val Pro Lys Ile Thr Leu Ile Ile Gly Gly Ser Tyr Gly Ala Gly
435 440 445

Asn Tyr Gly Met Cys Gly Arg Ala Tyr Ser Pro Arg Phe Leu Tyr Ile
450 455 460

Trp Pro Asn Ala Arg Ile Ser Val Met Gly Gly Glu Gln Ala Ala Asn
465 470 475 480

Val Leu Ala Thr Ile Thr Lys Asp Gln Arg Ala Arg Glu Gly Lys Gln
485 490 495

Phe Ser Ser Ala Asp Glu Ala Ala Leu Lys Glu Pro Ile Ile Lys Lys
500 505 510

Phe Glu Glu Glu Gly Asn Pro Tyr Tyr Ser Ser Ala Arg Val Trp Asp
515 520 525

Asp Gly Ile Ile Asp Pro Ala Asp Thr Arg Leu Val Leu Gly Leu Ser
530 535 540

Phe Ser Ala Ala Leu Asn Ala Pro Ile Glu Lys Thr Asp Phe Gly Ile

545 550 555 560

Phe Arg Met

<210> 306
<211> 53
<212> PRT
<213> Homo sapiens

<400> 306
Met Val Gln Phe Glu Val Ile Phe Leu Leu Phe Gly Leu Cys Phe Ser
1 5 10 15

Ser Ser Ser Ser Arg Leu Val Gly Ser Gln Val Glu Asn Phe Ser Pro
20 25 30

Thr Pro Cys Ile Phe Gln Ala Phe Arg Cys Ser Ser Leu Ala Ile Ile
35 40 45

Ser Met Ser Leu Ser
50

<210> 307
<211> 421
<212> PRT
<213> Homo sapiens

<400> 307
Met Thr Val Phe Phe Lys Thr Leu Arg Asn His Trp Lys Lys Thr Thr
1 5 10 15

Ala Gly Leu Cys Leu Leu Thr Trp Gly Gly His Trp Leu Tyr Gly Lys
20 25 30

His Cys Asp Asn Leu Leu Arg Arg Ala Ala Cys Gln Glu Ala Gln Val
35 40 45

Phe Gly Asn Gln Leu Ile Pro Pro Asn Ala Gln Val Lys Lys Ala Thr
50 55 60

Val Phe Ser Ile Leu Gln Leu Ala Lys Glu Lys Pro Gly Leu Tyr Leu
65 70 75 80

Lys Lys Met Leu Pro Asp Phe Thr Phe Ile Trp His Gly Cys Asp Tyr
85 90 95

Cys Lys Thr Asp Tyr Glu Gly Gln Ala Lys Lys Leu Leu Glu Leu Met
100 105 110

Glu Asn Thr Asp Val Ile Ile Val Ala Gly Gly Asp Gly Thr Leu Gln
115 120 125

Glu Val Val Thr Gly Val Leu Arg Arg Thr Asp Glu Ala Thr Phe Ser
130 135 140

Lys Ile Pro Ile Gly Phe Ile Pro Leu Gly Glu Thr Ser Ser Leu Ser

145 150 155 160

His Thr Leu Phe Ala Glu Ser Gly Asn Lys Val Gln His Ile Thr Asp
165 170 175

Ala Thr Leu Ala Ile Val Lys Gly Glu Thr Val Pro Leu Asp Val Leu
180 185 190

Gln Ile Lys Gly Glu Lys Glu Gln Pro Val Phe Ala Met Thr Gly Leu
195 200 205

Arg Trp Gly Ser Phe Arg Asp Ala Gly Val Lys Val Ser Lys Tyr Trp
210 215 220

Tyr Leu Gly Pro Leu Lys Ile Lys Ala Ala His Phe Phe Ser Thr Leu
225 230 235 240

Lys Glu Trp Pro Gln Thr His Gln Ala Ser Ile Ser Tyr Thr Gly Pro
245 250 255

Thr Glu Arg Pro Pro Asn Glu Pro Glu Glu Thr Pro Val Gln Arg Pro
260 265 270

Ser Leu Tyr Arg Arg Ile Leu Arg Arg Leu Ala Ser Tyr Trp Ala Gln
275 280 285

Pro Gln Asp Ala Leu Ser Gln Glu Val Ser Pro Glu Val Trp Lys Asp
290 295 300

Val Gln Leu Ser Thr Ile Glu Leu Ser Ile Thr Thr Arg Asn Asn Gln
305 310 315 320

Leu Asp Pro Thr Ser Lys Glu Asp Phe Leu Asn Ile Cys Ile Glu Pro
325 330 335

Asp Thr Ile Ser Lys Gly Asp Phe Ile Thr Ile Gly Ser Arg Lys Val
340 345 350

Arg Asn Pro Lys Leu His Val Glu Gly Thr Glu Cys Leu Gln Ala Ser
355 360 365

Gln Cys Thr Leu Leu Ile Pro Glu Gly Ala Gly Gly Ser Phe Ser Ile
370 375 380

Asp Ser Glu Glu Tyr Glu Ala Met Pro Val Glu Val Lys Leu Leu Pro
385 390 395 400

Arg Lys Leu Gln Phe Phe Cys Asp Pro Arg Lys Arg Glu Gln Met Leu
405 410 415

Thr Ser Pro Thr Gln
420

<210> 308
<211> 242
<212> PRT
<213> Homo sapiens

<400> 308

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Met Gln Leu Gly Ser Val Leu Leu Thr Arg Cys Pro Phe Trp Gly Cys
1               5                   10                  15

Phe Ser Gln Leu Met Leu Tyr Ala Glu Arg Ala Glu Ala Arg Arg Lys
            20                  25                  30

Pro Asp Ile Pro Val Pro Tyr Leu Tyr Phe Asp Met Gly Ala Ala Val
        35                  40                  45

Leu Cys Ala Ser Phe Met Ser Phe Gly Val Lys Arg Arg Trp Phe Ala
    50                  55                  60

Leu Gly Ala Ala Leu Gln Leu Ala Ile Ser Thr Tyr Ala Ala Tyr Ile
65                  70                  75                  80

Gly Gly Tyr Val His Tyr Gly Asp Trp Leu Lys Val Arg Met Tyr Ser
                85                  90                  95

Arg Thr Val Ala Ile Ile Gly Gly Phe Leu Val Leu Ala Ser Gly Ala
            100                 105                 110

Gly Glu Leu Tyr Arg Arg Lys Pro Arg Ser Arg Ser Leu Gln Ser Thr
        115                 120                 125

Gly Gln Val Phe Leu Gly Ile Tyr Leu Ile Cys Val Ala Tyr Ser Leu
    130                 135                 140

Gln His Ser Lys Glu Asp Arg Leu Ala Tyr Leu Asn His Leu Pro Gly
145                 150                 155                 160

Gly Glu Leu Met Ile Gln Leu Phe Phe Val Leu Tyr Gly Ile Leu Ala
                165                 170                 175

Leu Ala Phe Leu Ser Gly Tyr Tyr Val Thr Leu Ala Ala Gln Ile Leu
            180                 185                 190

Ala Val Leu Leu Pro Pro Val Met Leu Leu Ile Asp Gly Asn Val Ala
        195                 200                 205

Tyr Trp His Asn Thr Arg Arg Val Glu Phe Trp Asn Gln Met Lys Leu
    210                 215                 220

Leu Gly Glu Ser Val Gly Ile Phe Gly Thr Ala Val Ile Leu Ala Thr
225                 230                 235                 240

Asp Gly
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<210> 309
<211> 189
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (94)
<223> Xaa equals any amino acid

<400> 309

Met Ala Leu Leu Ser Arg Pro Ala Leu Thr Leu Leu Leu Leu Leu Met
1 5 10 15

Ala Ala Val Val Arg Cys Gln Glu Gln Ala Gln Thr Thr Asp Trp Arg
20 25 30

Ala Thr Leu Lys Thr Ile Arg Asn Gly Val His Lys Ile Asp Thr Tyr
35 40 45

Leu Asn Ala Ala Leu Asp Leu Leu Gly Gly Glu Asp Gly Leu Cys Gln
50 55 60

Tyr Lys Cys Ser Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys
65 70 75 80

Pro Ser Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Xaa His Leu
85 90 95

Asn Ile Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg
100 105 110

Cys Tyr Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe
115 120 125

Gln Tyr Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly
130 135 140

Leu Thr Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe
145 150 155 160

Asp Ser Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg
165 170 175

Ala Ala Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
180 185

<210> 310
<211> 64
<212> PRT
<213> Homo sapiens

<400> 310
Met Pro Leu Phe Leu Phe Val Ala His Leu Ile Ser Leu Leu Leu Ala
1 5 10 15

Phe Arg Arg Pro Pro Ala Ser Gln Ile Thr Pro Arg Ala Trp Thr Thr
20 25 30

Glu Ile Ala Ser Cys Glu Ser Val Glu Met Val Lys Ala Leu Ser Ser
35 40 45

Leu Arg Ser Arg Ala Gln Val Asn Ala Asp Phe Pro Gly His Leu Cys
50 55 60

<210> 311
<211> 49
<212> PRT
<213> Homo sapiens

<400> 311
Met Asn Leu Leu Gly Met Ile Phe Ser Met Cys Gly Leu Met Leu Lys
1 5 10 15

Leu Lys Trp Cys Ala Trp Val Ala Val Tyr Cys Ser Phe Ile Ser Phe
20 25 30

Ala Asn Ser Arg Ser Ser Glu Asp Thr Lys Gln Met Met Ser Ser Phe
35 40 45

Met

<210> 312
<211> 59
<212> PRT
<213> Homo sapiens

<400> 312
Met Asn Ser Thr Leu Cys Val Val Leu Ser Leu Met Cys Met Asn Ser
1 5 10 15

Thr Leu Cys Val Val Leu Ser Leu Thr His Ser Cys Pro Ser Pro Gln
20 25 30

Val Pro Lys Val His Tyr Met Ile Phe Met Pro Leu His Leu His Ser
35 40 45

Leu Ala Leu Thr Gln Leu Ile Ile Ile Tyr Lys
50 55

<210> 313
<211> 240
<212> PRT
<213> Homo sapiens

<400> 313
Met Gly Asn Cys Gln Ala Gly His Asn Leu His Leu Cys Leu Ala His
1 5 10 15

His Pro Pro Leu Val Cys Ala Thr Leu Ile Leu Leu Leu Leu Gly Leu
20 25 30

Ser Gly Leu Gly Leu Gly Ser Phe Leu Leu Thr His Arg Thr Gly Leu
35 40 45

Arg Ser Pro Asp Ile Pro Gln Asp Trp Val Ser Phe Leu Arg Ser Phe
50 55 60

Gly Gln Leu Thr Leu Cys Pro Arg Asn Gly Thr Val Thr Gly Lys Trp
65 70 75 80

Arg Gly Ser His Val Val Gly Leu Leu Thr Thr Leu Asn Phe Gly Asp
85 90 95

Gly Pro Asp Arg Asn Lys Thr Arg Thr Phe Gln Ala Thr Val Leu Gly
100 105 110

Ser Gln Met Gly Leu Lys Gly Ser Ser Ala Gly Gln Leu Val Leu Ile
115 120 125

Thr Ala Arg Val Thr Thr Glu Arg Thr Ala Gly Thr Cys Leu Tyr Phe
130 135 140

Ser Ala Val Pro Gly Ile Leu Pro Ser Ser Gln Pro Pro Ile Ser Cys
145 150 155 160

Ser Glu Glu Gly Ala Gly Asn Ala Thr Leu Ser Pro Arg Met Gly Glu
165 170 175

Glu Cys Val Ser Val Trp Ser His Glu Gly Leu Val Leu Thr Lys Leu
180 185 190

Leu Thr Ser Glu Glu Leu Ala Leu Cys Gly Ser Arg Leu Leu Val Leu
195 200 205

Gly Ser Phe Leu Leu Leu Phe Cys Gly Leu Leu Cys Cys Val Thr Ala
210 215 220

Met Cys Phe His Pro Arg Arg Glu Ser His Trp Ser Arg Thr Arg Leu
225 230 235 240

<210> 314
<211> 39
<212> PRT
<213> Homo sapiens

<400> 314
Met Leu Leu Leu Leu Lys Thr Leu Phe Val Thr Phe Trp Ser Thr Asn
1 5 10 15

Leu Ser Ile Thr Phe Ser Asn Tyr Asn Val Lys Leu Tyr Gln Trp Gln
20 25 30

Ser Tyr Ile Val Asn Gly Ser
35

<210> 315
<211> 174
<212> PRT
<213> Homo sapiens

<400> 315
Met Glu Ala Pro Gly Pro Arg Ala Leu Arg Thr Ala Leu Cys Gly Gly
1 5 10 15

Cys Cys Cys Leu Leu Leu Cys Ala Gln Leu Ala Val Ala Gly Lys Gly
20 25 30

Ala Arg Gly Phe Gly Arg Gly Ala Leu Ile Arg Leu Asn Ile Trp Pro
35 40 45

Ala Val Gln Gly Ala Cys Lys Gln Leu Glu Val Cys Glu His Cys Val
50 55 60

Glu Gly Asp Arg Ala Arg Asn Leu Ser Ser Cys Met Trp Glu Gln Cys
65 70 75 80

Arg Pro Glu Glu Pro Gly His Cys Val Ala Gln Ser Glu Val Val Lys
85 90 95

Glu Gly Cys Ser Ile Tyr Asn Arg Ser Glu Ala Cys Pro Ala Ala His
100 105 110

His His Pro Thr Tyr Glu Pro Lys Thr Val Thr Thr Gly Ser Pro Pro
115 120 125

Val Pro Glu Ala His Ser Pro Gly Phe Asp Gly Ala Ser Phe Ile Gly
130 135 140

Gly Val Val Leu Val Leu Ser Leu Gln Ala Val Ala Phe Phe Val Leu
145 150 155 160

His Phe Leu Lys Ala Lys Asp Ser Thr Tyr Gln Thr Leu Ile
165 170

<210> 316
<211> 61
<212> PRT
<213> Homo sapiens

<400> 316
Met Tyr Leu Phe Leu Lys Thr Leu Leu Ser Phe Ser Thr Leu Met Met
1 5 10 15

Thr Thr Ala Leu Ser Phe Met Val Ile Thr Val Leu Trp Val Leu Leu
20 25 30

Leu His Leu Leu Ala Asn Ile Cys Ile Pro Arg Lys Cys Ser Phe Ala
35 40 45

Cys Phe Tyr Ile Asn Gly Ile Leu Leu His Ala Val Phe
50 55 60

<210> 317
<211> 319
<212> PRT
<213> Homo sapiens

<400> 317
Met Ser Trp Cys Cys Leu Trp Leu Cys Leu Ser Ser Val Gly Arg Thr
1 5 10 15

Gly Ser Ala Gly Pro Ser Leu Pro Phe Ser Glu Leu Cys Ser Leu Gly
20 25 30

Leu Leu Arg Leu Arg Pro Val Phe Ser Pro Leu His Ser Gly Pro Gly
35 40 45

Lys Pro Ala Gln Phe Leu Ala Gly Glu Ala Glu Glu Val Asn Ala Phe
50 55 60

Ala Leu Gly Phe Leu Ser Thr Ser Ser Gly Val Ser Gly Glu Asp Glu
65 70 75 80

Val Glu Pro Leu His Asp Gly Val Glu Glu Ala Glu Lys Lys Met Glu
85 90 95

Glu Glu Gly Val Ser Val Ser Glu Met Glu Ala Thr Gly Ala Gln Gly
100 105 110

Pro Ser Arg Val Glu Glu Ala Glu Gly His Thr Glu Val Thr Glu Ala
115 120 125

Glu Gly Ser Gln Gly Thr Ala Glu Ala Asp Gly Pro Gly Ala Ser Ser
130 135 140

Gly Asp Glu Asp Ala Ser Gly Arg Ala Ala Ser Pro Glu Ser Ala Ser
145 150 155 160

Ser Thr Pro Glu Ser Leu Gln Ala Arg Arg His His Gln Phe Leu Glu
165 170 175

Pro Ala Pro Ala Pro Gly Ala Ala Val Leu Ser Ser Glu Pro Ala Glu
180 185 190

Pro Leu Leu Val Arg His Pro Pro Arg Pro Arg Thr Thr Gly Pro Arg
195 200 205

Pro Arg Gln Asp Pro His Lys Ala Gly Leu Ser His Tyr Val Lys Leu
210 215 220

Phe Ser Phe Tyr Ala Lys Met Pro Met Glu Arg Lys Ala Leu Glu Met
225 230 235 240

Val Glu Lys Cys Leu Asp Lys Tyr Phe Gln His Leu Cys Asp Asp Leu
245 250 255

Glu Val Phe Ala Ala His Ala Gly Arg Lys Thr Val Lys Pro Glu Asp
260 265 270

Leu Glu Leu Leu Met Arg Arg Gln Gly Leu Val Thr Asp Gln Val Ser
275 280 285

Leu His Val Leu Val Glu Arg His Leu Pro Leu Glu Tyr Arg Gln Leu
290 295 300

Leu Ile Pro Cys Ala Tyr Ser Gly Asn Ser Val Phe Pro Ala Gln
305 310 315

<210> 318
<211> 336

<212> PRT
<213> Homo sapiens

<400> 318

```
Met Ile Ser Tyr Ile Val Leu Leu Ser Ile Leu Leu Trp Pro Leu Val
 1               5                  10                  15

Val Tyr His Glu Leu Ile Gln Arg Met Tyr Thr Arg Leu Glu Pro Leu
            20                  25                  30

Leu Met Gln Leu Asp Tyr Ser Met Lys Ala Glu Ala Asn Ala Leu His
        35                  40                  45

His Lys His Asp Lys Arg Lys Arg Gln Gly Lys Asn Ala Pro Pro Gly
    50                  55                  60

Gly Asp Glu Pro Leu Ala Glu Thr Glu Ser Glu Ser Glu Ala Glu Leu
65                  70                  75                  80

Ala Gly Phe Ser Pro Val Val Asp Val Lys Lys Thr Ala Leu Ala Leu
                85                  90                  95

Ala Ile Thr Asp Ser Glu Leu Ser Asp Glu Glu Ala Ser Ile Leu Glu
            100                 105                 110

Ser Gly Gly Phe Ser Val Ser Arg Ala Thr Thr Pro Gln Leu Thr Asp
        115                 120                 125

Val Ser Glu Asp Leu Asp Gln Gln Ser Leu Pro Ser Glu Pro Glu Glu
    130                 135                 140

Thr Leu Ser Arg Asp Leu Gly Glu Gly Glu Glu Gly Glu Leu Ala Pro
145                 150                 155                 160

Pro Glu Asp Leu Leu Gly Arg Pro Gln Ala Leu Ser Arg Gln Ala Leu
                165                 170                 175

Asp Ser Glu Glu Glu Glu Glu Asp Val Ala Ala Lys Glu Thr Leu Leu
            180                 185                 190

Arg Leu Ser Ser Pro Leu His Phe Val Asn Thr His Phe Asn Gly Ala
        195                 200                 205

Gly Ser Pro Gln Asp Gly Val Lys Cys Ser Pro Gly Gly Pro Val Glu
    210                 215                 220

Thr Leu Ser Pro Glu Thr Val Ser Gly Gly Leu Thr Ala Leu Pro Gly
225                 230                 235                 240

Thr Leu Ser Pro Pro Leu Cys Leu Val Gly Ser Asp Pro Ala Pro Ser
                245                 250                 255

Pro Ser Ile Leu Pro Pro Val Pro Gln Asp Ser Pro Gln Pro Leu Pro
            260                 265                 270

Ala Pro Glu Glu Glu Glu Ala Leu Thr Thr Glu Asp Phe Glu Leu Leu
        275                 280                 285

Asp Gln Gly Glu Leu Glu Gln Leu Asn Ala Glu Leu Gly Leu Glu Pro
    290                 295                 300
```

Glu Thr Pro Pro Lys Pro Pro Asp Ala Pro Pro Leu Gly Pro Asp Ile
305 310 315 320

His Ser Leu Val Gln Ser Asp Gln Glu Ala Gln Ala Val Ala Glu Pro
325 330 335

<210> 319
<211> 272
<212> PRT
<213> Homo sapiens

<400> 319
Met Trp Gly Asn Lys Phe Gly Val Leu Leu Phe Leu Tyr Ser Val Leu
1 5 10 15

Leu Thr Lys Gly Ile Glu Asn Ile Lys Asn Glu Ile Glu Asp Ala Ser
20 25 30

Glu Pro Leu Ile Asp Pro Val Tyr Gly His Gly Ser Gln Ser Leu Ile
35 40 45

Asn Leu Leu Leu Thr Gly His Ala Val Ser Asn Val Trp Asp Gly Asp
50 55 60

Arg Glu Cys Ser Gly Met Lys Leu Leu Gly Ile His Glu Gln Ala Ala
65 70 75 80

Val Gly Phe Leu Thr Leu Met Glu Ala Leu Arg Tyr Cys Lys Val Gly
85 90 95

Ser Tyr Leu Lys Ser Pro Lys Phe Pro Ile Trp Ile Val Gly Ser Glu
100 105 110

Thr His Leu Thr Val Phe Phe Ala Lys Asp Met Ala Leu Val Ala Pro
115 120 125

Glu Ala Pro Ser Glu Gln Ala Arg Arg Val Phe Gln Thr Tyr Asp Pro
130 135 140

Glu Asp Asn Gly Phe Ile Pro Asp Ser Leu Leu Glu Asp Val Met Lys
145 150 155 160

Ala Leu Asp Leu Val Ser Asp Pro Glu Tyr Ile Asn Leu Met Lys Asn
165 170 175

Lys Leu Asp Pro Glu Gly Leu Gly Ile Ile Leu Leu Gly Pro Phe Leu
180 185 190

Gln Glu Phe Phe Pro Asp Gln Gly Ser Ser Gly Pro Glu Ser Phe Thr
195 200 205

Val Tyr His Tyr Asn Gly Leu Lys Gln Ser Asn Tyr Asn Glu Lys Val
210 215 220

Met Tyr Val Glu Gly Thr Ala Val Val Met Gly Phe Glu Asp Pro Met
225 230 235 240

Leu Gln Thr Asp Asp Thr Pro Ile Lys Arg Cys Leu Gln Thr Lys Trp
245 250 255

Pro Tyr Ile Glu Leu Leu Trp Thr Thr Asp Arg Ser Pro Ser Leu Asn
260 265 270

<210> 320
<211> 89
<212> PRT
<213> Homo sapiens

<400> 320
Met Phe Lys Asp Tyr Pro Pro Ala Ile Lys Pro Ser Tyr Asp Val Leu
1 5 10 15

Leu Leu Leu Leu Leu Leu Val Leu Leu Leu Gln Ala Gly Leu Asn Thr
20 25 30

Gly Thr Ala Ile Gln Cys Val Arg Phe Lys Val Ser Ala Arg Leu Gln
35 40 45

Gly Ala Ser Trp Asp Thr Gln Asn Gly Pro Gln Glu Arg Leu Ala Gly
50 55 60

Glu Val Ala Arg Ser Pro Leu Lys Glu Phe Asp Lys Glu Lys Ala Trp
65 70 75 80

Arg Ala Val Val Val Gln Met Ala Gln
85

<210> 321
<211> 51
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (23)
<223> Xaa equals any amino acid

<400> 321
Met Ala Gln His His Leu Leu Ser Ile Leu Leu Ala Ile Leu Ser Cys
1 5 10 15

Ser Ser Gln Pro Arg Gln Xaa Arg Gly Ser Gly Ala Leu Pro Cys Glu
20 25 30

Val Cys Ser Ala Val Leu Leu Thr Cys Leu Arg Lys Ile Ser Gly Ser
35 40 45

Leu Cys Val
50

<210> 322
<211> 74
<212> PRT
<213> Homo sapiens

<400> 322
Met Leu His Leu Ala Ala Met Trp Trp Ala Cys Val Thr Thr Leu Val
1 5 10 15

Phe Thr Leu Val Ser Lys Leu Phe Ile Pro Leu Lys Ser Ser Met Asp
20 25 30

Gly Glu Met Ser Leu Asp Pro His Ser Cys Val Leu Val Cys Ile Cys
35 40 45

Phe Pro Leu Arg Phe Val Phe Val Ser Cys Phe Glu Leu Tyr Leu Val
50 55 60

Gln Ser Ile Val Lys Leu Ser Gln Gln Leu
65 70

<210> 323
<211> 127
<212> PRT
<213> Homo sapiens

<400> 323
Met Gly Gln Val Trp Arg Val Pro Pro Leu Leu Leu Ser Val Gln Val
1 5 10 15

Phe Leu Thr Met Ala His Ala Phe His Gln Ala Pro Glu Leu Gln Trp
20 25 30

Leu Gly Leu Trp Phe Trp Val Arg Leu Phe Ala Gly Gly Asp Gly Gly
35 40 45

Leu His Leu Asn Ile Ser Ser Val Thr Leu Pro Leu Leu His Gly Lys
50 55 60

Gln Leu Ser Arg Glu Val Pro Ser Cys Gln Gly Lys Pro Arg Leu Gly
65 70 75 80

Arg Pro Pro Tyr Lys Glu Pro Gln Asp Cys Ser His Gly Cys His Leu
85 90 95

Ser Trp Lys Gly Arg Phe Met Gly Phe Pro Gly Thr Pro Arg Leu Ser
100 105 110

Trp Pro Arg Gly Lys Arg Trp Leu Leu Gln Glu Phe Asp Leu Ser
115 120 125

<210> 324
<211> 215
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (83)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (141)
<223> Xaa equals any amino acid

<400> 324

```
Met Tyr Gly Lys Ser Ser Thr Arg Ala Val Leu Leu Leu Leu Gly Ile
  1               5                  10                  15

Gln Leu Thr Ala Leu Trp Pro Ile Ala Ala Val Glu Ile Tyr Thr Ser
             20                  25                  30

Arg Val Leu Glu Ala Val Asn Gly Thr Asp Ala Arg Leu Lys Cys Thr
         35                  40                  45

Phe Ser Ser Phe Ala Pro Val Gly Asp Ala Leu Thr Val Thr Trp Asn
     50                  55                  60

Phe Arg Pro Leu Asp Gly Gly Pro Glu Gln Phe Val Phe Tyr Tyr His
 65                  70                  75                  80

Ile Asp Xaa Phe Gln Pro Met Ser Gly Arg Phe Lys Asp Arg Val Ser
                 85                  90                  95

Trp Asp Gly Asn Pro Glu Arg Tyr Asp Ala Ser Ile Leu Leu Trp Lys
            100                 105                 110

Leu Gln Phe Asp Asp Asn Gly Thr Tyr Thr Cys Gln Val Lys Asn Pro
        115                 120                 125

Pro Asp Val Asp Gly Val Ile Gly Asp Ile Arg Leu Xaa Val Val His
    130                 135                 140

Thr Val Arg Phe Ser Glu Ile His Phe Leu Ala Leu Ala Ile Gly Ser
145                 150                 155                 160

Ala Cys Ala Leu Met Ile Ile Ile Val Ile Val Val Val Leu Phe Gln
                165                 170                 175

His Tyr Arg Lys Lys Arg Trp Ala Glu Arg Ala His Lys Val Val Glu
            180                 185                 190

Ile Lys Ser Lys Glu Glu Glu Arg Leu Asn Gln Glu Lys Lys Val Ser
        195                 200                 205

Val Tyr Leu Glu Asp Thr Asp
    210                 215
```

<210> 325
<211> 47
<212> PRT
<213> Homo sapiens

<400> 325
Met Phe Tyr Pro Pro Cys Pro Phe Phe Pro Gln Leu Cys Phe Cys Ile
1 5 10 15

Phe Phe Leu Gly Lys Cys Lys Leu Ser Leu Ser Phe Met Thr Cys Glu
20 25 30

Ile Ser Val Ser Leu Glu Phe Val Arg Arg Arg Gly Asn His Ala
35 40 45

<210> 326
<211> 100
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (36)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (47)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (51)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (83)
<223> Xaa equals any amino acid

<400> 326
Met Gly Met Ile Leu Val Leu Ala Ser Phe Leu Ala His Pro Val Glu
1 5 10 15

Ala Leu Ala Gln Ala Val Ala Leu Gly Gln Gln Gln Leu Ala Leu Leu
20 25 30

Gly Val Gln Xaa His Ala Val Glu Gly Phe Leu Gln Leu Gln Xaa Cys
35 40 45

Phe Ala Xaa Leu Phe Val Phe Glu Gly Ala Leu Leu Ala His Leu Gly
50 55 60

His Phe Phe Val Glu Pro Gly Ala Ala Gln Gly Gln Leu Leu Asp Leu
65 70 75 80

Gly Leu Xaa Arg Arg Glu Leu Gly Phe Gln Phe Ala Leu Leu Ala Arg
85 90 95

Phe Val Leu Gln
100

<210> 327
<211> 40
<212> PRT
<213> Homo sapiens

<400> 327
Met Ile Ile Leu His Ile Val Val Cys Leu Phe Thr Ile Ser Ile Ile
1 5 10 15

Glu Glu Gln Lys Glu Glu Ile Leu Cys Ser Thr Lys Ser Gln Ala Glu
20 25 30

Lys Thr Val Thr His Ile Glu Gln
35 40

<210> 328
<211> 108
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (62)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (63)
<223> Xaa equals any amino acid

<400> 328
Met Gly Ala Ala Lys Val Trp Gly Glu Val Gly Arg Trp Leu Val Ile
1 5 10 15

Ala Leu Ile Gln Leu Ala Lys Ala Val Leu Arg Met Leu Leu Leu Leu
20 25 30

Trp Phe Lys Ala Gly Leu Gln Thr Ser Pro Pro Ile Val Pro Leu Asp
35 40 45

Arg Glu Thr Arg His Ser Pro Arg Met Val Thr Thr Ala Xaa Xaa Thr
50 55 60

Met Ser Ser Pro Thr Trp Gly Ser Gly Gln Thr Gly Trp Cys Glu Pro
65 70 75 80

Ser Arg Thr Arg Arg Pro Cys Thr Pro Gly Thr Gly Glu Leu Pro Ser
85 90 95

Ser Gly Arg Asp Gly Ser Ser Ser Ile Thr Arg Ser
100 105

<210> 329
<211> 941
<212> PRT
<213> Homo sapiens

<400> 329
Met Val Phe Leu Pro Leu Lys Trp Ser Leu Ala Thr Met Ser Phe Leu
1 5 10 15

Leu Ser Ser Leu Leu Ala Leu Leu Thr Val Ser Thr Pro Ser Trp Cys
20 25 30

Gln Ser Thr Glu Ala Ser Pro Lys Arg Ser Asp Gly Thr Pro Phe Pro
35 40 45

Trp Asn Lys Ile Arg Leu Pro Glu Tyr Val Ile Pro Val His Tyr Asp
50 55 60

Leu Leu Ile His Ala Asn Leu Thr Thr Leu Thr Phe Trp Gly Thr Thr
65 70 75 80

Lys Val Glu Ile Thr Ala Ser Gln Pro Thr Ser Thr Ile Ile Leu His
85 90 95

Ser His His Leu Gln Ile Ser Arg Ala Thr Leu Arg Lys Gly Ala Gly
100 105 110

Glu Arg Leu Ser Glu Glu Pro Leu Gln Val Leu Glu His Pro Pro Gln
115 120 125

Glu Gln Ile Ala Leu Leu Ala Pro Glu Pro Leu Leu Val Gly Leu Pro
130 135 140

Tyr Thr Val Val Ile His Tyr Ala Gly Asn Leu Ser Glu Thr Phe His
145 150 155 160

Gly Phe Tyr Lys Ser Thr Tyr Arg Thr Lys Glu Gly Glu Leu Arg Ile
165 170 175

Leu Ala Ser Thr Gln Phe Glu Pro Thr Ala Ala Arg Met Ala Phe Pro
180 185 190

Cys Phe Asp Glu Pro Ala Phe Lys Ala Ser Phe Ser Ile Lys Ile Arg
195 200 205

Arg Glu Pro Arg His Leu Ala Ile Ser Asn Met Pro Leu Val Lys Ser
210 215 220

Val Thr Val Ala Glu Gly Leu Ile Glu Asp His Phe Asp Val Thr Val
225 230 235 240

Lys Met Ser Thr Tyr Leu Val Ala Phe Ile Ile Ser Asp Phe Glu Ser
245 250 255

Val Ser Lys Ile Thr Lys Ser Gly Val Lys Val Ser Val Tyr Ala Val
260 265 270

Pro Asp Lys Met Asn Gln Ala Asp Tyr Ala Leu Asp Ala Ala Val Thr
275 280 285

Leu Leu Glu Phe Tyr Glu Asp Tyr Phe Ser Ile Pro Tyr Pro Leu Pro
290 295 300

Lys Gln Asp Leu Ala Ala Ile Pro Asp Phe Gln Ser Gly Ala Met Glu
305 310 315 320

```
Asn Trp Gly Leu Thr Thr Tyr Arg Glu Ser Ala Leu Leu Phe Asp Ala
                325                 330                 335

Glu Lys Ser Ser Ala Ser Ser Lys Leu Gly Ile Thr Met Thr Val Ala
            340                 345                 350

His Glu Leu Ala His Gln Trp Phe Gly Asn Leu Val Thr Met Glu Trp
        355                 360                 365

Trp Asn Asp Leu Trp Leu Asn Glu Gly Phe Ala Lys Phe Met Glu Phe
    370                 375                 380

Val Ser Val Ser Val Thr His Pro Glu Leu Lys Val Gly Asp Tyr Phe
385                 390                 395                 400

Phe Gly Lys Cys Phe Asp Ala Met Glu Val Asp Ala Leu Asn Ser Ser
                405                 410                 415

His Pro Val Ser Thr Pro Val Glu Asn Pro Ala Gln Ile Arg Glu Met
            420                 425                 430

Phe Asp Asp Val Ser Tyr Asp Lys Gly Ala Cys Ile Leu Asn Met Leu
        435                 440                 445

Arg Glu Tyr Leu Ser Ala Asp Ala Phe Lys Ser Gly Ile Val Gln Tyr
    450                 455                 460

Leu Gln Lys His Ser Tyr Lys Asn Thr Lys Asn Glu Asp Leu Trp Asp
465                 470                 475                 480

Ser Met Ala Ser Ile Cys Pro Thr Asp Gly Val Lys Gly Met Asp Gly
                485                 490                 495

Phe Cys Ser Arg Ser Gln His Ser Ser Ser Ser Ser His Trp His Gln
            500                 505                 510

Glu Gly Val Asp Val Lys Thr Met Met Asn Thr Trp Thr Leu Gln Arg
        515                 520                 525

Gly Phe Pro Leu Ile Thr Ile Thr Val Arg Gly Arg Asn Val His Met
    530                 535                 540

Lys Gln Glu His Tyr Met Lys Gly Ser Asp Gly Ala Pro Asp Thr Gly
545                 550                 555                 560

Tyr Leu Trp His Val Pro Leu Thr Phe Ile Thr Ser Lys Ser Asp Met
                565                 570                 575

Val His Arg Phe Leu Leu Lys Thr Lys Thr Asp Val Leu Ile Leu Pro
            580                 585                 590

Glu Glu Val Glu Trp Ile Lys Phe Asn Val Gly Met Asn Gly Tyr Tyr
        595                 600                 605

Ile Val His Tyr Glu Asp Asp Gly Trp Asp Ser Leu Thr Gly Leu Leu
    610                 615                 620

Lys Gly Thr His Thr Ala Val Ser Ser Asn Asp Arg Ala Ser Leu Ile
625                 630                 635                 640
```

Asn Asn Ala Phe Gln Leu Val Ser Ile Gly Lys Leu Ser Ile Glu Lys
645 650 655

Ala Leu Asp Leu Ser Leu Tyr Leu Lys His Glu Thr Glu Ile Met Pro
660 665 670

Val Phe Gln Gly Leu Asn Glu Leu Ile Pro Met Tyr Lys Leu Met Glu
675 680 685

Lys Arg Asp Met Asn Glu Val Glu Thr Gln Phe Lys Ala Phe Leu Ile
690 695 700

Arg Leu Leu Arg Asp Leu Ile Asp Lys Gln Thr Trp Thr Asp Glu Gly
705 710 715 720

Ser Val Ser Glu Arg Met Leu Arg Ser Glu Leu Leu Leu Leu Ala Cys
725 730 735

Val His Asn Tyr Gln Pro Cys Val Gln Arg Ala Glu Gly Tyr Phe Arg
740 745 750

Lys Trp Lys Glu Ser Asn Gly Asn Leu Ser Leu Pro Val Asp Val Thr
755 760 765

Leu Ala Val Phe Ala Val Gly Ala Gln Ser Thr Glu Gly Trp Asp Phe
770 775 780

Leu Tyr Ser Lys Tyr Gln Phe Ser Leu Ser Ser Thr Glu Lys Ser Gln
785 790 795 800

Ile Glu Phe Ala Leu Cys Arg Thr Gln Asn Lys Glu Lys Leu Gln Trp
805 810 815

Leu Leu Asp Glu Ser Phe Lys Gly Asp Lys Ile Lys Thr Gln Glu Phe
820 825 830

Pro Gln Ile Leu Thr Leu Ile Gly Arg Asn Pro Val Gly Tyr Pro Leu
835 840 845

Ala Trp Gln Phe Leu Arg Lys Asn Trp Asn Lys Leu Val Gln Lys Phe
850 855 860

Glu Leu Gly Ser Ser Ser Ile Ala His Met Val Met Gly Thr Thr Asn
865 870 875 880

Gln Phe Ser Thr Arg Thr Arg Leu Glu Glu Val Lys Gly Phe Phe Ser
885 890 895

Ser Leu Lys Glu Asn Gly Ser Gln Leu Arg Cys Val Gln Gln Thr Ile
900 905 910

Glu Thr Ile Glu Glu Asn Ile Gly Trp Met Asp Lys Asn Phe Asp Lys
915 920 925

Ile Arg Val Trp Leu Gln Ser Glu Lys Leu Glu Arg Met
930 935 940

<210> 330
<211> 267

<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (172)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (175)
<223> Xaa equals any amino acid

<400> 330
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Met Ser Glu Ile Arg Gly Lys Pro Ile Glu Ser Ser Cys Met Tyr Gly
  1               5                  10                  15

Thr Cys Cys Leu Trp Gly Lys Thr Tyr Ser Ile Gly Phe Leu Arg Phe
             20                  25                  30

Cys Lys Gln Ala Thr Leu Gln Phe Cys Val Val Lys Pro Leu Met Ala
         35                  40                  45

Val Ser Thr Val Val Leu Gln Ala Phe Gly Lys Tyr Arg Asp Gly Asp
     50                  55                  60

Phe Asp Val Thr Ser Gly Tyr Leu Tyr Val Thr Ile Ile Tyr Asn Ile
 65                  70                  75                  80

Ser Val Ser Leu Ala Leu Tyr Ala Leu Phe Leu Phe Tyr Phe Ala Thr
                 85                  90                  95

Arg Glu Leu Leu Ser Pro Tyr Ser Pro Val Leu Lys Phe Phe Met Val
            100                 105                 110

Lys Ser Val Ile Phe Leu Ser Phe Trp Gln Gly Met Leu Leu Ala Ile
        115                 120                 125

Leu Glu Lys Cys Gly Ala Ile Pro Lys Ile His Ser Ala Arg Val Ser
    130                 135                 140

Val Gly Glu Gly Thr Val Ala Ala Gly Tyr Gln Asp Phe Ile Ile Cys
145                 150                 155                 160

Val Glu Met Phe Phe Ala Ala Leu Ala Leu Arg Xaa Ala Phe Xaa Tyr
                165                 170                 175

Lys Val Tyr Ala Asp Lys Arg Leu Asp Ala Gln Gly Arg Cys Ala Pro
            180                 185                 190

Met Lys Ser Ile Ser Ser Ser Leu Lys Glu Thr Met Asn Pro His Asp
        195                 200                 205

Ile Val Gln Asp Ala Ile His Asn Phe Ser Pro Ala Tyr Gln Gln Tyr
    210                 215                 220

Thr Gln Gln Ser Thr Leu Glu Pro Gly Pro Thr Trp Arg Gly Gly Ala
225                 230                 235                 240

His Gly Leu Ser Arg Ser His Ser Leu Ser Gly Ala Arg Asp Asn Glu
                245                 250                 255
```

Lys Thr Leu Leu Leu Ser Ser Asp Asp Glu Phe
260 265

<210> 331
<211> 53
<212> PRT
<213> Homo sapiens

<400> 331
Met Leu Val Leu Met Thr Thr Cys Ile Leu Ala Ala Val Cys Val His
1 5 10 15

Thr Ala Gln Cys Ala Pro Asp Ser Arg Met Asp Asn Asp Cys Pro Ser
20 25 30

His Gln Ala Gln Ile His Phe Arg Ala Ser Glu Val Arg Arg Gly Trp
35 40 45

Thr Phe Asn His Asp
50

<210> 332
<211> 52
<212> PRT
<213> Homo sapiens

<400> 332
Met His Cys His Ser Ala Leu Gly Pro Met Ser Thr Pro Val Leu Pro
1 5 10 15

Phe Ser Gly Ile Gly Leu Ala Phe Leu Cys Leu Cys Leu Ala Ala Ser
20 25 30

Met Val Asp Leu Lys Cys Leu Gly Met Asn Ser Thr Leu Leu Gln Pro
35 40 45

Ser Ile Lys Glu
50

<210> 333
<211> 87
<212> PRT
<213> Homo sapiens

<400> 333
Met Gly Leu His Leu Arg Pro Tyr Arg Val Gly Leu Leu Pro Asp Gly
1 5 10 15

Leu Leu Phe Leu Leu Leu Leu Leu Met Leu Leu Ala Asp Pro Ala Leu
20 25 30

Pro Ala Gly Arg His Pro Pro Val Val Leu Val Pro Gly Asp Leu Gly
35 40 45

Asn Gln Leu Glu Ala Lys Leu Asp Lys Pro Thr Val Val His Tyr Leu
50 55 60

Cys Ser Lys Lys Thr Glu Ser Tyr Phe Thr Ile Trp Leu Asn Leu Glu
65 70 75 80

Leu Leu Leu Pro Val His His
85

<210> 334
<211> 40
<212> PRT
<213> Homo sapiens

<400> 334
Met Gly Pro Ser Gln Arg Glu Val Thr Val Gln Trp His Arg Ala Leu
1 5 10 15

Phe Leu Leu Pro Leu Leu Leu Leu Ser Thr Arg Thr Glu Thr Lys Asn
20 25 30

Phe Gly Phe Lys Trp Leu Lys Asp
35 40

<210> 335
<211> 525
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (210)
<223> Xaa equals any amino acid

<400> 335
Met Leu Ala Phe Pro Leu Leu Leu Thr Gly Leu Ile Ser Phe Arg Glu
1 5 10 15

Lys Arg Leu Gln Asp Val Gly Thr Pro Ala Ala Arg Ala Arg Ala Phe
20 25 30

Phe Thr Ala Pro Val Val Val Phe His Leu Asn Ile Leu Ser Tyr Phe
35 40 45

Ala Phe Leu Cys Leu Phe Ala Tyr Val Leu Met Val Asp Phe Gln Pro
50 55 60

Val Pro Ser Trp Cys Glu Cys Ala Ile Tyr Leu Trp Leu Phe Ser Leu
65 70 75 80

Val Cys Glu Glu Met Arg Gln Leu Phe Tyr Asp Pro Asp Glu Cys Gly
85 90 95

Leu Met Lys Lys Ala Ala Leu Tyr Phe Ser Asp Phe Trp Asn Lys Leu
100 105 110

Asp Val Gly Ala Ile Leu Leu Phe Val Ala Gly Leu Thr Cys Arg Leu

115 120 125

Ile Pro Ala Thr Leu Tyr Pro Gly Arg Val Ile Leu Ser Leu Asp Phe
130 135 140

Ile Leu Phe Cys Leu Arg Leu Met His Ile Phe Thr Ile Ser Lys Thr
145 150 155 160

Leu Gly Pro Lys Ile Ile Ile Val Lys Arg Met Met Lys Asp Val Phe
165 170 175

Phe Phe Leu Phe Leu Leu Ala Val Trp Val Val Ser Phe Gly Val Ala
180 185 190

Lys Gln Ala Ile Leu Ile His Asn Glu Arg Arg Val Asp Trp Leu Phe
195 200 205

Arg Xaa Ala Val Tyr His Ser Tyr Leu Thr Ile Phe Gly Gln Ile Pro
210 215 220

Gly Tyr Ile Asp Gly Val Asn Phe Asn Pro Glu His Cys Ser Pro Asn
225 230 235 240

Gly Thr Asp Pro Tyr Lys Pro Lys Cys Pro Glu Ser Asp Ala Thr Gln
245 250 255

Gln Arg Pro Ala Phe Pro Glu Trp Leu Thr Val Leu Leu Leu Cys Leu
260 265 270

Tyr Leu Leu Phe Thr Asn Ile Leu Leu Leu Asn Leu Leu Ile Ala Met
275 280 285

Phe Asn Tyr Thr Phe Gln Gln Val Gln Glu His Thr Asp Gln Ile Trp
290 295 300

Lys Phe Gln Arg His Asp Leu Ile Glu Glu Tyr His Gly Arg Pro Ala
305 310 315 320

Ala Pro Pro Pro Phe Ile Leu Leu Ser His Leu Gln Leu Phe Ile Lys
325 330 335

Arg Val Val Leu Lys Thr Pro Ala Lys Arg His Lys Gln Leu Lys Asn
340 345 350

Lys Leu Glu Lys Asn Glu Glu Ala Ala Leu Leu Ser Trp Glu Ile Tyr
355 360 365

Leu Lys Glu Asn Tyr Leu Gln Asn Arg Gln Phe Gln Gln Lys Gln Arg
370 375 380

Pro Glu Gln Lys Ile Glu Asp Ile Ser Asn Lys Val Asp Ala Met Val
385 390 395 400

Asp Leu Leu Asp Leu Asp Pro Leu Lys Arg Ser Gly Ser Met Glu Gln
405 410 415

Arg Leu Ala Ser Leu Glu Glu Gln Val Ala Gln Thr Ala Arg Ala Leu
420 425 430

His Trp Ile Val Arg Thr Leu Arg Ala Ser Gly Phe Ser Ser Glu Ala
435 440 445

Asp Val Pro Thr Leu Ala Ser Gln Lys Ala Ala Glu Glu Pro Asp Ala
450 455 460

Glu Pro Gly Gly Arg Lys Lys Thr Glu Glu Pro Gly Asp Ser Tyr His
465 470 475 480

Val Asn Ala Arg His Leu Leu Tyr Pro Asn Cys Pro Val Thr Arg Phe
485 490 495

Pro Val Pro Asn Glu Lys Val Pro Trp Glu Thr Glu Phe Leu Ile Tyr
500 505 510

Asp Pro Pro Phe Tyr Thr Ala Glu Arg Lys Asp Ala Ala
515 520 525

<210> 336
<211> 937
<212> PRT
<213> Homo sapiens

<400> 336
Met Gln Asn Ser Gly Lys Thr Lys Phe Lys Arg Thr Ser Ile Asp Arg
1 5 10 15

Leu Met Asn Thr Leu Val Leu Trp Ile Phe Gly Phe Leu Ile Cys Leu
20 25 30

Gly Ile Ile Leu Ala Ile Gly Asn Ser Ile Trp Glu Ser Gln Thr Gly
35 40 45

Asp Gln Phe Arg Thr Phe Leu Phe Trp Asn Glu Gly Glu Lys Ser Ser
50 55 60

Val Phe Ser Gly Phe Leu Thr Phe Trp Ser Tyr Ile Ile Ile Leu Asn
65 70 75 80

Thr Val Val Pro Ile Ser Leu Tyr Val Ser Val Glu Val Ile Arg Leu
85 90 95

Gly His Ser Tyr Phe Ile Asn Trp Asp Arg Lys Met Tyr Tyr Ser Arg
100 105 110

Lys Ala Ile Pro Ala Val Ala Arg Thr Thr Thr Leu Asn Glu Glu Leu
115 120 125

Gly Gln Ile Glu Tyr Ile Phe Ser Asp Lys Thr Gly Thr Leu Thr Gln
130 135 140

Asn Ile Met Thr Phe Lys Arg Cys Ser Ile Asn Gly Arg Ile Tyr Gly
145 150 155 160

Glu Val His Asp Asp Leu Asp Gln Lys Thr Glu Ile Thr Gln Glu Lys
165 170 175

Glu Pro Val Asp Phe Ser Val Lys Ser Gln Ala Asp Arg Glu Phe Gln
180 185 190

Phe Phe Asp His Asn Leu Met Glu Ser Ile Lys Met Gly Asp Pro Lys

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        195                 200                 205

Val His Glu Phe Leu Arg Leu Leu Ala Leu Cys His Thr Val Met Ser
    210                 215                 220

Glu Glu Asn Ser Ala Gly Glu Leu Ile Tyr Gln Val Gln Ser Pro Asp
225                 230                 235                 240

Glu Gly Ala Leu Val Thr Ala Ala Arg Asn Phe Gly Phe Ile Phe Lys
                245                 250                 255

Ser Arg Thr Pro Glu Thr Ile Thr Ile Glu Glu Leu Gly Thr Leu Val
            260                 265                 270

Thr Tyr Gln Leu Leu Ala Phe Leu Asp Phe Asn Asn Thr Arg Lys Arg
        275                 280                 285

Met Ser Val Ile Val Arg Asn Pro Glu Gly Gln Ile Lys Leu Tyr Ser
    290                 295                 300

Lys Gly Ala Asp Thr Ile Leu Phe Glu Lys Leu His Pro Ser Asn Glu
305                 310                 315                 320

Val Leu Leu Ser Leu Thr Ser Asp His Leu Ser Glu Phe Ala Gly Glu
                325                 330                 335

Gly Leu Arg Thr Leu Ala Ile Ala Tyr Arg Asp Leu Asp Asp Lys Tyr
            340                 345                 350

Phe Lys Glu Trp His Lys Met Leu Glu Asp Ala Asn Val Ala Thr Glu
        355                 360                 365

Glu Arg Asp Glu Arg Ile Ala Gly Leu Tyr Glu Glu Ile Glu Arg Asp
    370                 375                 380

Leu Met Leu Leu Gly Ala Thr Ala Val Glu Asp Lys Leu Gln Glu Gly
385                 390                 395                 400

Val Ile Glu Thr Val Thr Ser Leu Ser Leu Ala Asn Ile Lys Ile Trp
                405                 410                 415

Val Leu Thr Gly Asp Lys Gln Glu Thr Ala Ile Asn Ile Gly Tyr Ala
            420                 425                 430

Cys Asn Met Leu Thr Asp Asp Met Asn Asp Val Phe Val Ile Ala Gly
        435                 440                 445

Asn Asn Ala Val Glu Val Arg Glu Glu Leu Arg Lys Ala Lys Gln Asn
    450                 455                 460

Leu Phe Gly Gln Asn Arg Asn Phe Ser Asn Gly His Val Val Cys Glu
465                 470                 475                 480

Lys Lys Gln Gln Leu Glu Leu Asp Ser Ile Val Glu Glu Thr Ile Thr
                485                 490                 495

Gly Asp Tyr Ala Leu Ile Ile Asn Gly His Ser Leu Ala His Ala Leu
            500                 505                 510

Glu Ser Asp Val Lys Asn Asp Leu Leu Glu Leu Ala Cys Met Cys Lys
        515                 520                 525
```

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Thr Val Ile Cys Cys Arg Val Thr Pro Leu Gln Lys Ala Gln Val Val
    530                 535                 540

Glu Leu Val Lys Lys Tyr Arg Asn Ala Val Thr Leu Ala Ile Gly Asp
545                 550                 555                 560

Gly Ala Asn Asp Val Ser Met Ile Lys Ser Ala His Ile Gly Val Gly
                565                 570                 575

Ile Ser Gly Gln Glu Gly Leu Gln Ala Val Leu Ala Ser Asp Tyr Ser
            580                 585                 590

Phe Ala Gln Phe Arg Tyr Leu Gln Arg Leu Leu Leu Val His Gly Arg
        595                 600                 605

Trp Ser Tyr Phe Arg Met Cys Lys Phe Leu Cys Tyr Phe Phe Tyr Lys
    610                 615                 620

Asn Phe Ala Phe Thr Leu Val His Phe Trp Phe Gly Phe Phe Cys Gly
625                 630                 635                 640

Phe Ser Ala Gln Thr Val Tyr Asp Gln Trp Phe Ile Thr Leu Phe Asn
                645                 650                 655

Ile Val Tyr Thr Ser Leu Pro Val Leu Ala Met Gly Ile Phe Asp Gln
            660                 665                 670

Asp Val Ser Asp Gln Asn Ser Val Asp Cys Pro Gln Leu Tyr Lys Pro
        675                 680                 685

Gly Gln Leu Asn Leu Leu Phe Asn Lys Arg Lys Phe Phe Ile Cys Val
    690                 695                 700

Met His Gly Ile Tyr Thr Ser Leu Val Leu Phe Phe Ile Pro Tyr Gly
705                 710                 715                 720

Ala Phe Tyr Asn Val Ala Gly Glu Asp Gly Gln His Ile Ala Asp Tyr
                725                 730                 735

Gln Ser Phe Ala Val Thr Met Ala Thr Ser Leu Val Ile Val Val Ser
            740                 745                 750

Val Gln Ile Ala Leu Asp Thr Ser Tyr Trp Thr Phe Ile Asn His Val
        755                 760                 765

Phe Ile Trp Gly Ser Ile Ala Ile Tyr Phe Ser Ile Leu Phe Thr Met
    770                 775                 780

His Ser Asn Gly Ile Phe Gly Ile Phe Pro Asn Gln Phe Pro Phe Val
785                 790                 795                 800

Gly Asn Ala Arg His Ser Leu Thr Gln Lys Cys Ile Trp Leu Val Ile
                805                 810                 815

Leu Leu Thr Thr Val Ala Ser Val Met Pro Val Val Ala Phe Arg Phe
            820                 825                 830

Leu Lys Val Asp Leu Tyr Pro Thr Leu Ser Asp Gln Ile Arg Arg Trp
        835                 840                 845
```

Gln Lys Ala Gln Lys Lys Ala Arg Pro Pro Ser Ser Arg Arg Pro Arg
850 855 860

Thr Arg Arg Ser Ser Ser Arg Arg Ser Gly Tyr Ala Phe Ala His Gln
865 870 875 880

Glu Gly Tyr Gly Glu Leu Ile Thr Ser Gly Lys Asn Met Arg Ala Lys
885 890 895

Asn Pro Pro Pro Thr Ser Gly Leu Glu Lys Thr His Tyr Asn Ser Thr
900 905 910

Ser Trp Ile Glu Asn Leu Cys Lys Lys Thr Thr Asp Thr Val Ser Ser
915 920 925

Phe Ser Gln Asp Lys Thr Val Lys Leu
930 935

<210> 337
<211> 122
<212> PRT
<213> Homo sapiens

<400> 337
Met Ile Gly Gly Ile Thr Cys Ile Leu Ser Leu Ile Cys Ala Leu Ala
1 5 10 15

Leu Ala Tyr Leu Asp Gln Arg Ala Glu Arg Ile Leu His Lys Glu Gln
20 25 30

Gly Lys Thr Gly Glu Val Ile Lys Leu Thr Asp Val Lys Asp Phe Ser
35 40 45

Leu Pro Leu Trp Leu Ile Phe Ile Ile Cys Val Cys Tyr Tyr Val Ala
50 55 60

Val Phe Pro Phe Ile Gly Leu Gly Lys Val Phe Phe Thr Glu Lys Phe
65 70 75 80

Gly Phe Ser Ser Gln Ala Ala Ser Ala Ile Asn Ser Val Val Tyr Val
85 90 95

Ile Ser Ala Pro Met Ser Pro Val Phe Gly Leu Leu Val Asp Lys Thr
100 105 110

Gly Lys Asn Ile Ile Trp Val Leu Cys Ala
115 120

<210> 338
<211> 46
<212> PRT
<213> Homo sapiens

<400> 338
Met Pro Trp Leu Lys Ser Leu Leu His Phe Ser Leu Phe Leu Val Val
1 5 10 15

Phe Ser Thr Leu Ala Val Lys Ser Leu Gly Val Pro Val Ala Ala Gly
20 25 30

Ser Pro Phe Cys Ile Val Asp Val Leu His Phe Ile Leu Leu
35 40 45

<210> 339
<211> 66
<212> PRT
<213> Homo sapiens

<400> 339
Met Ser Trp Val Ile Val Val Ile Ile Trp Gly Tyr Leu Leu Glu Gly
1 5 10 15

His Gly Val Pro Phe Cys Lys Ser Tyr Gly Pro Ser Pro Trp Lys Leu
20 25 30

His Thr His His Ala Ala Tyr Asn Ser Gly Ser Ser Gln Val Tyr Arg
35 40 45

Ile Leu Glu Thr Leu Met Ser Gly Ser Thr His Cys Ser Phe Ser Gly
50 55 60

Thr Phe
65

<210> 340
<211> 90
<212> PRT
<213> Homo sapiens

<400> 340
Met Pro Arg Ala Pro Trp Arg Ile Pro Leu Cys Ala Leu Pro Thr Leu
1 5 10 15

Cys Leu Gly Ser Pro Leu Pro Ser Gln Pro Thr His Pro Ile Phe Tyr
20 25 30

Asp His Arg Ala Pro Thr Trp Lys Met Ala His Pro Gly Gly Pro Arg
35 40 45

Ser Ser His Ser Pro Arg Thr Trp Arg Thr Pro Ser Ser Gln Thr Lys
50 55 60

Ala Ala Leu Pro Ala Gly Gly Ala Arg Asn Ser Pro Leu Gln Leu Cys
65 70 75 80

Thr Arg Ser Arg Phe Cys Gly Thr Pro Met
85 90

<210> 341
<211> 710
<212> PRT
<213> Homo sapiens

<400> 341
Met Pro Val Pro Trp Phe Leu Leu Ser Leu Ala Leu Gly Arg Ser Pro
1   5   10   15

Val Val Leu Ser Leu Glu Arg Leu Val Gly Pro Gln Asp Ala Thr His
            20   25   30

Cys Ser Pro Gly Leu Ser Cys Arg Leu Trp Asp Ser Asp Ile Leu Cys
        35   40   45

Leu Pro Gly Asp Ile Val Pro Ala Pro Gly Pro Val Leu Ala Pro Thr
    50   55   60

His Leu Gln Thr Glu Leu Val Leu Arg Cys Gln Lys Glu Thr Asp Cys
65   70   75   80

Asp Leu Cys Leu Arg Val Ala Val His Leu Ala Val His Gly His Trp
                85   90   95

Glu Glu Pro Glu Asp Glu Glu Lys Phe Gly Gly Ala Ala Asp Leu Gly
            100   105   110

Val Glu Glu Pro Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu Ser
        115   120   125

Phe Gln Ala Tyr Pro Thr Ala Arg Cys Val Leu Leu Glu Val Gln Val
    130   135   140

Pro Ala Ala Leu Val Gln Phe Gly Gln Ser Val Gly Ser Val Val Tyr
145   150   155   160

Asp Cys Phe Glu Ala Ala Leu Gly Ser Glu Val Arg Ile Trp Ser Tyr
                165   170   175

Thr Gln Pro Arg Tyr Glu Lys Glu Leu Asn His Thr Gln Gln Leu Pro
            180   185   190

Asp Cys Arg Gly Leu Glu Val Trp Asn Ser Ile Pro Ser Cys Trp Ala
        195   200   205

Leu Pro Trp Leu Asn Val Ser Ala Asp Gly Asp Asn Val His Phe Gly
    210   215   220

Leu Ser Leu Tyr Trp Asn Gln Val Gln Gly Pro Pro Lys Pro Arg Trp
225   230   235   240

His Lys Asn Leu Thr Gly Pro Gln Ile Ile Thr Leu Asn His Thr Asp
                245   250   255

Leu Val Pro Cys Leu Cys Ile Gln Val Trp Pro Leu Glu Pro Asp Ser
            260   265   270

Val Arg Thr Asn Ile Cys Pro Phe Arg Glu Asp Pro Arg Ala His Gln
        275   280   285

Asn Leu Trp Gln Ala Ala Arg Leu Arg Leu Leu Thr Leu Gln Ser Trp
    290   295   300

Leu Leu Asp Ala Pro Cys Ser Leu Pro Ala Glu Ala Ala Leu Cys Trp
305   310   315   320

```
Arg Ala Pro Gly Gly Asp Pro Cys Gln Pro Leu Val Pro Pro Leu Ser
                325                 330                 335

Trp Glu Asn Val Thr Val Asp Lys Val Leu Glu Phe Pro Leu Leu Lys
            340                 345                 350

Gly His Pro Asn Leu Cys Val Gln Val Asn Ser Ser Glu Lys Leu Gln
        355                 360                 365

Leu Gln Glu Cys Leu Trp Ala Asp Ser Leu Gly Pro Leu Lys Asp Asp
    370                 375                 380

Val Leu Leu Leu Glu Thr Arg Gly Pro Gln Asp Asn Arg Ser Leu Cys
385                 390                 395                 400

Ala Leu Glu Pro Ser Gly Cys Thr Ser Leu Pro Ser Lys Ala Ser Thr
                405                 410                 415

Arg Ala Ala Arg Leu Gly Glu Tyr Leu Leu Gln Asp Leu Gln Ser Gly
            420                 425                 430

Gln Cys Leu Gln Leu Trp Asp Asp Asp Leu Gly Ala Leu Trp Ala Cys
        435                 440                 445

Pro Met Asp Lys Tyr Ile His Lys Arg Trp Ala Leu Val Trp Leu Ala
    450                 455                 460

Cys Leu Leu Phe Ala Ala Ala Leu Ser Leu Ile Leu Leu Leu Lys Lys
465                 470                 475                 480

Asp His Ala Lys Gly Trp Leu Arg Leu Leu Lys Gln Asp Val Arg Ser
                485                 490                 495

Gly Ala Ala Ala Arg Gly Arg Ala Ala Leu Leu Leu Tyr Ser Ala Asp
            500                 505                 510

Asp Ser Gly Phe Glu Arg Leu Val Gly Ala Leu Ala Ser Ala Leu Cys
        515                 520                 525

Gln Leu Pro Leu Arg Val Ala Val Asp Leu Trp Ser Arg Arg Glu Leu
    530                 535                 540

Ser Ala Gln Gly Pro Val Ala Trp Phe His Ala Gln Arg Arg Gln Thr
545                 550                 555                 560

Leu Gln Glu Gly Gly Val Val Val Leu Leu Phe Ser Pro Gly Ala Val
                565                 570                 575

Ala Leu Cys Ser Glu Trp Leu Gln Asp Gly Val Ser Gly Pro Gly Ala
            580                 585                 590

His Gly Pro His Asp Ala Phe Arg Ala Ser Leu Ser Cys Val Leu Pro
        595                 600                 605

Asp Phe Leu Gln Gly Arg Ala Pro Gly Ser Tyr Val Gly Ala Cys Phe
    610                 615                 620

Asp Arg Leu Leu His Pro Asp Ala Val Pro Ala Leu Phe Arg Thr Val
625                 630                 635                 640
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Pro Val Phe Thr Leu Pro Ser Gln Leu Pro Asp Phe Leu Gly Ala Leu
645 650 655

Gln Gln Pro Arg Ala Pro Arg Ser Gly Arg Leu Gln Glu Arg Ala Glu
660 665 670

Gln Val Ser Arg Ala Leu Gln Pro Ala Leu Asp Ser Tyr Phe His Pro
675 680 685

Pro Gly Thr Pro Ala Pro Gly Arg Gly Val Gly Pro Gly Ala Gly Pro
690 695 700

Gly Ala Gly Asp Gly Thr
705 710

<210> 342
<211> 48
<212> PRT
<213> Homo sapiens

<400> 342
Met Phe Ala Pro Cys Phe Val Asn Leu Ala Leu Phe Tyr Leu Tyr Ile
1 5 10 15

Asn Ser Cys Asn Leu Leu Asn Leu Thr Ser Ile Asp Pro Phe Gln Gln
20 25 30

Lys Gly Lys Phe Lys Met Gln Thr Leu Leu Phe Ala Lys Glu Asp Ser
35 40 45

<210> 343
<211> 467
<212> PRT
<213> Homo sapiens

<400> 343
Met Leu Leu Leu Leu Leu Leu Pro Leu Leu Trp Gly Arg Glu Arg Val
1 5 10 15

Glu Gly Gln Lys Ser Asn Arg Lys Asp Tyr Ser Leu Thr Met Gln Ser
20 25 30

Ser Val Thr Val Gln Glu Gly Met Cys Val His Val Arg Cys Ser Phe
35 40 45

Ser Tyr Pro Val Asp Ser Gln Thr Asp Ser Asp Pro Val His Gly Tyr
50 55 60

Trp Phe Arg Ala Gly Asn Asp Ile Ser Trp Lys Ala Pro Val Ala Thr
65 70 75 80

Asn Asn Pro Ala Trp Ala Val Gln Glu Glu Thr Arg Asp Arg Phe His
85 90 95

Leu Leu Gly Asp Pro Gln Thr Lys Asn Cys Thr Leu Ser Ile Arg Asp
100 105 110

Ala Arg Met Ser Asp Ala Gly Arg Tyr Phe Phe Arg Met Glu Lys Gly
115 120 125

Asn Ile Lys Trp Asn Tyr Lys Tyr Asp Gln Leu Ser Val Asn Val Thr
130 135 140

Ala Leu Thr His Arg Pro Asn Ile Leu Ile Pro Gly Thr Leu Glu Ser
145 150 155 160

Gly Cys Phe Gln Asn Leu Thr Cys Ser Val Pro Trp Ala Cys Glu Gln
165 170 175

Gly Thr Pro Pro Met Ile Ser Trp Met Gly Thr Ser Val Ser Pro Leu
180 185 190

His Pro Ser Thr Thr Arg Ser Ser Val Leu Thr Leu Ile Pro Gln Pro
195 200 205

Gln His His Gly Thr Ser Leu Thr Cys Gln Val Thr Leu Pro Gly Ala
210 215 220

Gly Val Thr Thr Asn Arg Thr Ile Gln Leu Asn Val Ser Tyr Pro Pro
225 230 235 240

Gln Asn Leu Thr Val Thr Val Phe Gln Gly Glu Gly Thr Ala Ser Thr
245 250 255

Ala Leu Gly Asn Ser Ser Ser Leu Ser Val Leu Glu Gly Gln Ser Leu
260 265 270

Arg Leu Val Cys Ala Val Asp Ser Asn Pro Pro Ala Arg Leu Ser Trp
275 280 285

Thr Trp Arg Ser Leu Thr Leu Tyr Pro Ser Gln Pro Ser Asn Pro Leu
290 295 300

Val Leu Glu Leu Gln Val His Leu Gly Asp Glu Gly Glu Phe Thr Cys
305 310 315 320

Arg Ala Gln Asn Ser Leu Gly Ser Gln His Val Ser Leu Asn Leu Ser
325 330 335

Leu Gln Gln Glu Tyr Thr Gly Lys Met Arg Pro Val Ser Gly Val Leu
340 345 350

Leu Gly Ala Val Gly Gly Ala Gly Ala Thr Ala Leu Val Phe Leu Ser
355 360 365

Phe Cys Val Ile Phe Ile Val Val Arg Ser Cys Arg Lys Lys Ser Ala
370 375 380

Arg Pro Ala Ala Asp Val Gly Asp Ile Gly Met Lys Asp Ala Asn Thr
385 390 395 400

Ile Arg Gly Ser Ala Ser Gln Gly Asn Leu Thr Glu Ser Trp Ala Asp
405 410 415

Asp Asn Pro Arg His His Gly Leu Ala Ala His Ser Ser Gly Glu Glu

420 425 430

Arg Glu Ile Gln Tyr Ala Pro Leu Ser Phe His Lys Gly Glu Pro Gln
435 440 445

Asp Leu Ser Gly Gln Glu Ala Thr Asn Asn Glu Tyr Ser Glu Ile Lys
450 455 460

Ile Pro Lys
465

<210> 344
<211> 98
<212> PRT
<213> Homo sapiens

<400> 344
Met His Cys Cys Gln Leu Pro Trp Arg Cys Ala Gln Ala Pro Gln Glu
1 5 10 15

Ala Phe Leu Leu Cys Leu Leu Phe Leu Ile Leu Val Leu Val Leu Leu
20 25 30

Gly Cys Ser Arg Gly Leu Pro Gly His Thr Pro Trp Arg Leu His Pro
35 40 45

Ala Ala Ala Ala Leu Leu Ala Pro Leu Leu His Asp Ala Leu Gly Ala
50 55 60

Cys Gly Phe Gln Gly Pro Glu Tyr Leu Leu Pro Cys Leu Leu Pro Leu
65 70 75 80

Pro Lys Pro Gly Gln Leu Gln Gly Pro Trp Gly Pro Leu Trp Ala Leu
85 90 95

Leu Pro

<210> 345
<211> 365
<212> PRT
<213> Homo sapiens

<400> 345
Met Phe Val Gly Leu Met Ala Phe Leu Leu Ser Phe Tyr Leu Ile Phe
1 5 10 15

Thr Asn Glu Gly Arg Ala Leu Lys Thr Ala Thr Ser Leu Ala Glu Gly
20 25 30

Leu Ser Leu Val Val Ser Pro Asp Ser Ile His Ser Val Ala Pro Glu
35 40 45

Asn Glu Gly Arg Leu Val His Ile Ile Gly Ala Leu Arg Thr Ser Lys
50 55 60

Leu Leu Ser Asp Pro Asn Tyr Gly Val His Leu Pro Ala Val Lys Leu

```
65                  70                  75                  80

Arg Arg His Val Glu Met Tyr Gln Trp Val Glu Thr Glu Glu Ser Arg
                85                  90                  95

Glu Tyr Thr Glu Asp Gly Gln Val Lys Lys Glu Thr Arg Tyr Ser Tyr
            100                 105                 110

Asn Thr Glu Trp Arg Ser Glu Ile Ile Asn Ser Lys Asn Phe Asp Arg
        115                 120                 125

Glu Ile Gly His Lys Asn Pro Ser Ala Met Ala Val Glu Ser Phe Met
    130                 135                 140

Ala Thr Ala Pro Phe Val Gln Ile Gly Arg Phe Phe Leu Ser Ser Gly
145                 150                 155                 160

Leu Ile Asp Lys Val Asp Asn Phe Lys Ser Leu Ser Leu Ser Lys Leu
                165                 170                 175

Glu Asp Pro His Val Asp Ile Ile Arg Arg Gly Asp Phe Phe Tyr His
            180                 185                 190

Ser Glu Asn Pro Lys Tyr Pro Glu Val Gly Asp Leu Arg Val Ser Phe
        195                 200                 205

Ser Tyr Ala Gly Leu Ser Gly Asp Asp Pro Asp Leu Gly Pro Ala His
    210                 215                 220

Val Val Thr Val Ile Ala Arg Gln Arg Gly Asp Gln Leu Val Pro Phe
225                 230                 235                 240

Ser Thr Lys Ser Gly Asp Thr Leu Leu Leu Leu His His Gly Asp Phe
                245                 250                 255

Ser Ala Glu Glu Val Phe His Arg Glu Leu Arg Ser Asn Ser Met Lys
            260                 265                 270

Thr Trp Gly Leu Arg Ala Ala Gly Trp Met Ala Met Phe Met Gly Leu
        275                 280                 285

Asn Leu Met Thr Arg Ile Leu Tyr Thr Leu Val Asp Trp Phe Pro Val
    290                 295                 300

Phe Arg Asp Leu Val Asn Ile Gly Leu Lys Ala Phe Ala Phe Cys Val
305                 310                 315                 320

Ala Thr Ser Leu Thr Leu Leu Thr Val Ala Ala Gly Trp Leu Phe Tyr
                325                 330                 335

Arg Pro Leu Trp Ala Leu Leu Ile Ala Gly Leu Ala Leu Val Pro Ile
            340                 345                 350

Leu Val Ala Arg Thr Arg Val Pro Ala Lys Lys Leu Glu
        355                 360                 365
```

<210> 346
<211> 608
<212> PRT

<213> Homo sapiens

<220>
<221> SITE
<222> (265)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (597)
<223> Xaa equals any amino acid

<400> 346
```
Met Val Gly Thr Lys Leu Arg Gln Thr Lys Asp Ala Leu Phe Thr Ile
1               5                   10                  15

Leu His Asp Leu Arg Pro Gln Asp Arg Phe Ser Ile Ile Gly Phe Ser
            20                  25                  30

Asn Arg Ile Lys Val Trp Lys Asp His Leu Ile Ser Val Thr Pro Asp
        35                  40                  45

Ser Ile Arg Asp Gly Lys Val Tyr Ile His His Met Ser Pro Thr Gly
    50                  55                  60

Gly Thr Asp Ile Asn Gly Val Leu Gln Arg Ala Ile Arg Leu Leu Asn
65                  70                  75                  80

Lys Tyr Val Ala His Ser Gly Ile Gly Asp Arg Ser Val Ser Leu Ile
                85                  90                  95

Val Phe Leu Thr Asp Gly Lys Pro Thr Val Gly Glu Thr His Thr Leu
            100                 105                 110

Lys Ile Leu Asn Asn Thr Arg Glu Ala Ala Arg Gly Gln Val Cys Ile
        115                 120                 125

Phe Thr Ile Gly Ile Gly Asn Asp Val Asp Phe Arg Leu Leu Glu Lys
    130                 135                 140

Leu Ser Leu Glu Asn Cys Gly Leu Thr Arg Arg Val His Glu Glu Glu
145                 150                 155                 160

Asp Ala Gly Ser Gln Leu Ile Gly Phe Tyr Asp Glu Ile Arg Thr Pro
                165                 170                 175

Leu Leu Ser Asp Ile Arg Ile Asp Tyr Pro Pro Ser Ser Val Val Gln
            180                 185                 190

Ala Thr Lys Thr Leu Phe Pro Asn Tyr Phe Asn Gly Ser Glu Ile Ile
        195                 200                 205

Ile Ala Gly Lys Leu Val Asp Arg Lys Leu Asp His Leu His Val Glu
    210                 215                 220

Val Thr Ala Ser Asn Ser Lys Lys Phe Ile Ile Leu Lys Thr Asp Val
225                 230                 235                 240

Pro Val Arg Pro Gln Lys Ala Gly Lys Asp Val Thr Gly Ser Pro Arg
                245                 250                 255
```

Pro Gly Gly Asp Gly Glu Gly Asp Xaa Asn His Ile Glu Arg Leu Trp
260 265 270

Ser Tyr Leu Thr Thr Lys Glu Leu Leu Ser Ser Trp Leu Gln Ser Asp
275 280 285

Asp Glu Pro Glu Lys Glu Arg Leu Arg Gln Arg Ala Gln Ala Leu Ala
290 295 300

Val Ser Tyr Arg Phe Leu Thr Pro Phe Thr Ser Met Lys Leu Arg Gly
305 310 315 320

Pro Val Pro Arg Met Asp Gly Leu Glu Glu Ala His Gly Met Ser Ala
325 330 335

Ala Met Gly Pro Glu Pro Val Val Gln Ser Val Arg Gly Ala Gly Thr
340 345 350

Gln Pro Gly Pro Leu Leu Lys Lys Pro Tyr Gln Pro Arg Ile Lys Ile
355 360 365

Ser Lys Thr Ser Val Asp Gly Asp Pro His Phe Val Val Asp Phe Pro
370 375 380

Leu Ser Arg Leu Thr Val Cys Phe Asn Ile Asp Gly Gln Pro Gly Asp
385 390 395 400

Ile Leu Arg Leu Val Ser Asp His Arg Asp Ser Gly Val Thr Val Asn
405 410 415

Gly Glu Leu Ile Gly Ala Pro Ala Pro Pro Asn Gly His Lys Lys Gln
420 425 430

Arg Thr Tyr Leu Arg Thr Ile Thr Ile Leu Ile Asn Lys Pro Glu Arg
435 440 445

Ser Tyr Leu Glu Ile Thr Pro Ser Arg Val Ile Leu Asp Gly Gly Asp
450 455 460

Arg Leu Val Leu Pro Cys Asn Gln Ser Val Val Val Gly Ser Trp Gly
465 470 475 480

Leu Glu Val Ser Val Ser Ala Asn Ala Asn Val Thr Val Thr Ile Gln
485 490 495

Gly Ser Ile Ala Phe Val Ile Leu Ile His Leu Tyr Lys Lys Pro Ala
500 505 510

Pro Phe Gln Arg His His Leu Gly Phe Tyr Ile Ala Asn Ser Glu Gly
515 520 525

Leu Ser Ser Asn Cys His Gly Leu Leu Gly Gln Phe Leu Asn Gln Asp
530 535 540

Ala Arg Leu Thr Glu Asp Pro Ala Gly Pro Ser Gln Asn Leu Thr His
545 550 555 560

Pro Leu Leu Leu Gln Val Gly Glu Gly Pro Glu Ala Val Leu Thr Val
565 570 575

Lys Gly His Gln Val Pro Val Val Trp Lys Gln Arg Lys Ile Tyr Asn

580 585 590

Gly Glu Glu Gln Xaa Asp Cys Trp Phe Ala Arg Asn Met Pro Pro Asn
595 600 605

<210> 347
<211> 56
<212> PRT
<213> Homo sapiens

<400> 347
Met Phe Tyr Lys Leu Thr Leu Ile Leu Cys Glu Leu Ser Val Ala Gly
1 5 10 15

Val Thr Gln Ala Ala Ser Gln Arg Pro Leu Gln Arg Leu Pro Arg His
20 25 30

Ile Cys Ser Gln Arg Ser Ser Ser Trp Glu Met Pro Pro Gln Gly Pro
35 40 45

Ala Pro Asp His Val Gly Arg Ala
50 55

<210> 348
<211> 540
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (137)
<223> Xaa equals any amino acid

<400> 348
Met Val Arg Thr Asp Gly His Thr Leu Ser Glu Lys Arg Asn Tyr Gln
1 5 10 15

Val Thr Asn Ser Met Phe Gly Ala Ser Arg Lys Lys Phe Val Glu Gly
20 25 30

Val Asp Ser Asp Tyr His Asp Glu Asn Met Tyr Tyr Ser Gln Ser Ser
35 40 45

Met Phe Pro His Arg Ser Glu Lys Asp Met Leu Ala Ser Pro Ser Thr
50 55 60

Ser Gly Gln Leu Ser Gln Phe Gly Ala Ser Leu Tyr Gly Gln Gln Ser
65 70 75 80

Ala Leu Gly Leu Pro Met Arg Gly Met Ser Asn Asn Thr Pro Gln Leu
85 90 95

Asn Arg Ser Leu Ser Gln Gly Thr Gln Leu Pro Ser His Val Thr Pro
100 105 110

```
Thr Thr Gly Val Pro Thr Met Ser Leu His Thr Pro Pro Ser Pro Ser
        115                 120                 125

Arg Gly Ile Leu Pro Met Asn Pro Xaa Asn Met Met Asn His Ser Gln
    130                 135                 140

Val Gly Gln Gly Ile Gly Ile Pro Ser Arg Thr Asn Ser Met Ser Ser
145                 150                 155                 160

Ser Gly Leu Gly Ser Pro Asn Arg Ser Ser Pro Ser Ile Ile Cys Met
                165                 170                 175

Pro Lys Gln Gln Pro Ser Arg Gln Pro Phe Thr Val Asn Ser Met Ser
            180                 185                 190

Gly Phe Gly Met Asn Arg Asn Gln Ala Phe Gly Met Asn Asn Ser Leu
        195                 200                 205

Ser Ser Asn Ile Phe Asn Gly Thr Asp Gly Ser Glu Asn Val Thr Gly
    210                 215                 220

Leu Asp Leu Ser Asp Phe Pro Ala Leu Ala Asp Arg Asn Arg Arg Glu
225                 230                 235                 240

Gly Ser Gly Asn Pro Thr Pro Leu Ile Asn Pro Leu Ala Gly Arg Ala
                245                 250                 255

Pro Tyr Val Gly Met Val Thr Lys Pro Ala Asn Glu Gln Ser Gln Asp
            260                 265                 270

Phe Ser Ile His Asn Glu Asp Phe Pro Ala Leu Pro Gly Ser Ser Tyr
        275                 280                 285

Lys Asp Pro Thr Ser Ser Asn Asp Asp Ser Lys Ser Asn Leu Asn Thr
    290                 295                 300

Ser Gly Lys Thr Thr Ser Ser Thr Asp Gly Pro Lys Phe Pro Gly Asp
305                 310                 315                 320

Lys Ser Ser Thr Thr Gln Asn Asn Asn Gln Gln Lys Lys Gly Ile Gln
                325                 330                 335

Val Leu Pro Asp Gly Arg Val Thr Asn Ile Pro Gln Gly Met Val Thr
            340                 345                 350

Asp Gln Phe Gly Met Ile Gly Leu Leu Thr Phe Ile Arg Ala Ala Glu
        355                 360                 365

Thr Asp Pro Gly Met Val His Leu Ala Leu Gly Ser Asp Leu Thr Thr
    370                 375                 380

Leu Gly Leu Asn Leu Asn Ser Pro Glu Asn Leu Tyr Pro Lys Phe Ala
385                 390                 395                 400

Ser Pro Trp Ala Ser Ser Pro Cys Arg Pro Gln Asp Ile Asp Phe His
                405                 410                 415

Val Pro Ser Glu Tyr Leu Thr Asn Ile His Ile Arg Asp Lys Leu Ala
            420                 425                 430
```

Ala Ile Lys Leu Gly Arg Tyr Gly Glu Asp Leu Leu Phe Tyr Leu Tyr
435 440 445

Tyr Met Asn Gly Gly Asp Val Leu Gln Leu Leu Ala Ala Val Glu Leu
450 455 460

Phe Asn Arg Asp Trp Arg Tyr His Lys Glu Glu Arg Val Trp Ile Thr
465 470 475 480

Arg Ala Pro Gly Met Glu Pro Thr Met Lys Thr Asn Thr Tyr Glu Arg
485 490 495

Gly Thr Tyr Tyr Phe Phe Asp Cys Leu Asn Trp Arg Lys Val Ala Lys
500 505 510

Glu Phe His Leu Glu Tyr Asp Lys Leu Glu Glu Arg Pro His Leu Pro
515 520 525

Ser Thr Phe Asn Tyr Asn Pro Ala Gln Gln Ala Phe
530 535 540

<210> 349
<211> 99
<212> PRT
<213> Homo sapiens

<400> 349
Met Leu Phe Phe Leu Ser Leu Phe Leu Ser Leu Leu Leu Thr Leu Ser
1 5 10 15

Leu Pro Ser Phe Leu Pro Phe Ser Phe Phe Phe Phe Ser Leu Phe Pro
20 25 30

His Leu Ser Ala Cys Leu Leu Pro Ser Leu Pro Ser Pro Pro Phe Pro
35 40 45

Leu Pro Pro Ser Leu Pro Ser Phe Leu Pro Ser Phe Leu Pro Ser Phe
50 55 60

Leu Pro Ser Leu Leu Ser Pro Ser Phe Pro Ala Phe Phe Pro Ser Phe
65 70 75 80

Cys Gln Leu Ala Arg Arg Ser Pro Arg Lys Ser Thr Gln Met Leu Gln
85 90 95

Ser Thr Ser

<210> 350
<211> 66
<212> PRT
<213> Homo sapiens

<400> 350
Met Asn Tyr Ile Phe Leu Leu Met Ala Leu Pro His Leu Ile Ala Ile
1 5 10 15

Ala Leu Thr Trp Gly Arg Tyr Ser Phe Ser Cys Leu Ala Asn Lys Glu
20 25 30

Thr Glu Phe Gln Arg Cys Gln Val Thr Cys Leu Leu His Thr Leu Gly
35 40 45

Val Leu Met Phe Asn Phe Glu Leu Arg Ser Ile Trp Leu Glu Ser Ser
50 55 60

Leu His
65

<210> 351
<211> 72
<212> PRT
<213> Homo sapiens

<400> 351
Met Arg His Thr Cys Ile Val Asn Ile Ala Ala Ser Leu Leu Val Ala
1 5 10 15

Asn Thr Trp Phe Ile Val Val Ala Ala Ile Gln Asp Asn Arg Tyr Ile
20 25 30

Leu Cys Lys Thr Ala Cys Val Ala Ala Thr Phe Phe Ile His Phe Phe
35 40 45

Tyr Leu Ser Val Phe Phe Trp Met Leu Thr Leu Gly Pro His Ala Val
50 55 60

Leu Ser Pro Gly Phe His Ser Ala
65 70

<210> 352
<211> 41
<212> PRT
<213> Homo sapiens

<400> 352
Met Pro Pro Lys Gln Ile Pro Leu Thr Ser Leu Ser Leu Leu Ala Leu
1 5 10 15

Leu Leu Phe Phe Phe Phe Lys Ile Phe Cys Leu Leu Phe Leu Phe Tyr
20 25 30

Pro Leu Pro Asp Glu Ser Glu His Phe
35 40

<210> 353
<211> 47
<212> PRT
<213> Homo sapiens

<400> 353
Met Leu Ile Ser Val Asp Ser Asn Val Pro Val Val Phe Leu Leu Leu

```
  1               5                   10                  15

Phe Ile Leu Val Ile Leu Cys His Met Glu Cys Lys Gly His Ile Tyr
            20                  25                  30

Ile Cys Val Cys Val Cys Val Tyr Met Tyr Ile Phe Lys Asn Ile
        35                  40                  45
```

<210> 354
<211> 121
<212> PRT
<213> Homo sapiens

<400> 354

```
Met His Arg Ser Glu Pro Phe Leu Lys Met Ser Leu Leu Ile Leu Leu
  1               5                   10                  15

Phe Leu Gly Leu Ala Glu Ala Cys Thr Pro Arg Glu Val Asn Leu Leu
            20                  25                  30

Lys Gly Ile Ile Gly Leu Met Ser Arg Leu Ser Pro Asp Glu Ile Leu
        35                  40                  45

Gly Leu Leu Ser Leu Gln Val Leu His Glu Glu Thr Ser Gly Cys Lys
    50                  55                  60

Glu Glu Val Lys Pro Phe Ser Gly Thr Thr Pro Ser Arg Lys Pro Leu
 65                  70                  75                  80

Pro Lys Arg Lys Asn Thr Trp Asn Phe Leu Lys Cys Ala Tyr Met Val
                 85                  90                  95

Met Thr Tyr Leu Phe Val Ser Tyr Asn Lys Gly Asp Trp Phe Thr Phe
            100                 105                 110

Ser Ser Gln Val Leu Leu Pro Leu Leu
        115                 120
```

<210> 355
<211> 116
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (46)
<223> Xaa equals any amino acid

<400> 355

```
Met Pro Gly Gly Thr Arg Cys Arg Val Leu Leu Leu Ser Leu Thr Phe
  1               5                   10                  15

Gly Thr Ser Met Ala Cys Gly Asn Val Gly Leu Arg Leu Cys Pro Trp
            20                  25                  30

Thr Trp His Asn Trp Leu Leu Pro Pro His Leu Cys Ser Xaa Trp Pro
        35                  40                  45
```

Cys Arg Arg Cys Cys Trp Ala Ala Ala Thr Thr His Phe Ser Trp Pro
50 55 60

Pro Trp Val Arg Ser Ala Trp Gly Pro Pro Ala Ala Trp Leu Glu Ser
65 70 75 80

Ser Gly His Pro Leu Pro Ala Val Ala Ser Cys Ser Gln Pro Pro Ala
85 90 95

Ser Ala Asp Ser Ser Arg Phe Ser Lys Val Pro Cys Cys Arg Arg Arg
100 105 110

Gly Trp Thr Arg
115

<210> 356
<211> 86
<212> PRT
<213> Homo sapiens

<400> 356
Met Pro Trp His Val Cys Phe Phe Leu Ser Gly Leu Leu Phe Pro Ser
1 5 10 15

Pro Gln Thr Ser Leu Gln His Leu Cys Leu Leu Thr Ser Leu Ile Leu
20 25 30

Gly Val Thr Ile Ser Ala Tyr Glu His Ala Ile Asn Leu Pro Ser Leu
35 40 45

Gln Asn Ser Leu Leu Thr Ser His Pro Ser Val Ala Ala Leu Ser Leu
50 55 60

Leu Ser Ser Ser Leu Gln Gln Asn Ser Leu Lys Glu Leu Leu Ala Gly
65 70 75 80

His Ser Gly Ser Leu Leu
85

<210> 357
<211> 10
<212> PRT
<213> Homo sapiens

<400> 357
Gly Leu Leu Tyr Ile Met Tyr Cys Asn Ile
1 5 10

<210> 358
<211> 45
<212> PRT
<213> Homo sapiens

<400> 358

Met Val Lys Trp Ile Ile Leu Ser Cys Leu Ile Leu Lys Gly Lys Arg
1 5 10 15

Thr Leu Asn Ser Ser Thr Phe Tyr Ala Ala Asn Lys Ser Ser Thr Ile
20 25 30

Asn Arg Asn Leu Ser Trp Gln Ala Leu Pro Phe Thr His
35 40 45

<210> 359
<211> 38
<212> PRT
<213> Homo sapiens

<400> 359
Met Leu Lys Leu Ala Thr Ile Leu Leu Thr Leu Leu Leu Lys Asn Leu
1 5 10 15

Asp Ala Gly Leu Thr Asp Lys Leu Ser Arg Ser Asn Phe Ile Thr Asp
20 25 30

Phe Ile Leu Thr Lys Tyr
35

<210> 360
<211> 44
<212> PRT
<213> Homo sapiens

<400> 360
Met Pro Cys His Gly Leu Leu Ala Gln Gly Leu Ser Leu Ala Pro Leu
1 5 10 15

Pro Pro Trp Ala Leu Cys Cys Val Gly Val Ser Arg Ala Leu Gln Asp
20 25 30

Ile Gln Gln His Pro Arg Pro Pro Ala Pro Cys Gln
35 40

<210> 361
<211> 34
<212> PRT
<213> Homo sapiens

<400> 361
Met Gln Ala Arg Trp Phe His Ile Leu Gly Met Met Met Phe Ile Trp
1 5 10 15

Ser Ser Ala His Gln Tyr Lys Cys Pro Cys Tyr Ser Arg Gln Ser Gln
20 25 30

Glu Lys

<210> 362
<211> 68
<212> PRT
<213> Homo sapiens

<400> 362
Met Val His Asn Cys Leu Leu Leu Leu Lys Phe Leu Leu Leu Phe Cys
1   5   10   15

Phe Pro Leu Ile Ser Tyr Gln Leu Met Asn Gly Ser Leu Gln Ser Leu
            20   25   30

Gln Arg Leu Arg Met Ile Gln Asn Val Gln Cys Ile Val Leu Asn Lys
        35   40   45

Gln Glu Ala Glu Phe Leu Met Gly Ile Ser Phe Gln Ile Tyr Asp Trp
    50   55   60

Ser Leu Gly Phe
65

<210> 363
<211> 162
<212> PRT
<213> Homo sapiens

<400> 363
Met Thr Ser Asn Phe Pro Phe Cys Thr Leu Ile Leu Gly Ile Ala Gln
1   5   10   15

Ala Gln Ala Cys Pro Gly Cys Pro Gly Asp Trp Pro Gly Leu Gly Ser
            20   25   30

Gly Val Gly Glu Gly Leu His His Ile Arg Thr Cys Arg Thr Pro Ile
        35   40   45

Pro Cys Ser Pro Pro Ala Pro Ala Ala Ala Cys Leu Gly Ser Gly His
    50   55   60

Ala Arg Leu Pro Cys Val Leu Arg Leu Trp Pro Val Pro Ala Asn Leu
65   70   75   80

Ser Ser Pro Phe Arg Leu Glu Ala Leu His Cys Ser Phe Trp Ser Ser
                85   90   95

Pro Leu Leu Pro Ala Pro His Leu Ala Phe Phe Gly Phe Arg Asp Leu
            100   105   110

Leu Thr Asp Phe Leu Leu Ala Ala Cys Leu Leu Thr Phe Gln Lys Thr
        115   120   125

Pro Leu Glu Leu Pro Met Ala Val Val His Leu Leu Val Ala Thr Pro
    130   135   140

Cys Tyr Gln Met Leu Asp Asn Leu Pro Leu Pro Ser Ala Ala Ala Asn
145   150   155   160

Trp Cys

<210> 364
<211> 47
<212> PRT
<213> Homo sapiens

<400> 364
Met Leu Leu Phe Ser Ser Arg Phe Ile Met Phe Leu Trp Pro Pro Val
1 5 10 15

Ser Gly Val Cys Leu Ser Phe Ile Arg Asp Arg Ser Phe Leu Pro Met
20 25 30

Cys His Phe Ile Tyr Val Leu Ile Leu Cys Asn Ser Ile Ala Leu
35 40 45

<210> 365
<211> 79
<212> PRT
<213> Homo sapiens

<400> 365
Met Thr Leu Met Cys Leu Cys Leu Ser Val Thr Val Leu His Pro Leu
1 5 10 15

Arg Ser Lys Glu Arg Leu Ser Gly Thr Phe Cys Gly Tyr Ser Ser Ser
20 25 30

Trp Cys Ser Pro Ala Ser Glu Ser Ser Ser Pro Gly Ser Leu Leu Thr
35 40 45

Cys Ala Ala Ser Gly Ser His Pro Asp Cys Pro Leu Ser Gln Arg Leu
50 55 60

Leu Gly Val Gln Leu Ala Ala Leu Gly Arg Pro Gln Gly Leu Phe
65 70 75

<210> 366
<211> 292
<212> PRT
<213> Homo sapiens

<400> 366
Met Leu Arg Val Leu Cys Leu Leu Arg Pro Trp Arg Pro Leu Arg Ala
1 5 10 15

Arg Gly Cys Ala Ser Asp Gly Ala Ala Gly Gly Ser Glu Ile Gln Val
20 25 30

Arg Ala Leu Ala Gly Pro Asp Gln Gly Ile Thr Glu Ile Leu Met Asn
35 40 45

Arg Pro Ser Ala Arg Asn Ala Leu Gly Asn Val Phe Val Ser Glu Leu
50 55 60

Leu Glu Thr Leu Ala Gln Leu Arg Glu Asp Arg Gln Val Arg Val Leu
65   70   75   80

Leu Phe Arg Ser Gly Val Lys Gly Val Phe Cys Ala Gly Ala Asp Leu
                85   90   95

Lys Glu Arg Glu Gln Met Ser Glu Ala Glu Val Gly Val Phe Val Gln
            100   105   110

Arg Leu Arg Gly Leu Met Asn Asp Ile Ala Ala Phe Pro Ala Pro Thr
        115   120   125

Ile Ala Ala Met Asp Gly Phe Ala Leu Gly Gly Gly Leu Glu Leu Ala
    130   135   140

Leu Ala Cys Asp Leu Arg Val Ala Ala Ser Ser Ala Val Met Gly Leu
145   150   155   160

Ile Glu Thr Thr Arg Gly Leu Leu Pro Gly Ala Gly Gly Thr Gln Arg
                165   170   175

Leu Pro Arg Cys Leu Gly Val Ala Leu Ala Lys Glu Leu Ile Phe Thr
            180   185   190

Gly Arg Arg Leu Ser Gly Thr Glu Ala His Val Leu Gly Leu Val Asn
        195   200   205

His Ala Val Ala Gln Asn Glu Glu Gly Asp Ala Ala Tyr Gln Arg Ala
    210   215   220

Arg Ala Leu Ala Gln Glu Ile Leu Pro Gln Ala Pro Ile Ala Val Arg
225   230   235   240

Leu Gly Lys Val Ala Ile Asp Arg Gly Thr Glu Val Asp Ile Ala Ser
                245   250   255

Gly Met Ala Ile Glu Gly Met Cys Tyr Ala Gln Asn Ile Pro Thr Arg
            260   265   270

Asp Arg Leu Glu Gly Met Ala Ala Phe Arg Glu Lys Arg Thr Pro Lys
        275   280   285

Phe Val Gly Lys
    290

<210> 367
<211> 121
<212> PRT
<213> Homo sapiens

<400> 367
Met Ile Met Ala Gln Lys Ile Gly Gly Leu Thr Trp Trp Ala Ile Met
1   5   10   15

Phe Ile Ile Leu Phe Glu Ile Thr Gly Thr Ser Ser Ser Phe Leu Arg
            20   25   30

Ile Asn Ala Leu Pro His Phe Ser Met Asn Arg Cys Gly Glu Ala Tyr

35 40 45

Phe Pro Phe Ser Tyr Leu Tyr Thr Ser Leu Gln Lys Gln Phe Leu Met
50 55 60

Lys Val Ser Gly Ile Val Lys Asn Leu Arg Gly Asn Asp Asp Trp Arg
65 70 75 80

Cys Phe Gly Val Phe Phe Cys Ile His Phe Leu Met Arg Lys Val Leu
85 90 95

Asn Val Val Gln Val Arg Pro Asn Tyr Tyr Leu Thr Ile Ile Gly Arg
100 105 110

Phe Tyr Val Ser Val Lys Val Phe Lys
115 120

<210> 368
<211> 50
<212> PRT
<213> Homo sapiens

<400> 368
Met Tyr Ile Tyr Leu Ile His Leu Cys Met Cys Val Tyr Ile Tyr Ile
1 5 10 15

Tyr Ile Leu Leu Ile Ile Tyr Thr Leu Asp Pro Glu Pro Pro Ser Trp
20 25 30

Ser Pro Lys Leu Asp Ser His Leu Ser Leu Arg Gln Pro Ser Asn Asp
35 40 45

Arg Phe
50

<210> 369
<211> 44
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (11)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (34)
<223> Xaa equals any amino acid

<400> 369
Met Val Leu His Cys Ile Ala Trp Leu Gln Xaa Gly Ile Ser Phe Leu
1 5 10 15

Phe Leu Phe Leu Cys Val Ile Ala Ile Gly Ala Thr Asn Phe Ala Ser
20 25 30

Pro Xaa Phe Tyr Lys Leu Val Ser Ser Gly Val Ala
35 40

<210> 370
<211> 89
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (12)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (13)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (72)
<223> Xaa equals any amino acid

<400> 370
Met Ser Gly Gly Leu Ser Phe Leu Leu Leu Val Xaa Xaa Gly Thr Gln
1 5 10 15

Ser Pro Leu His Leu Ala Gly Ser Cys Pro Gly Gln Thr His Leu Ser
20 25 30

Phe Pro Leu Gly Gln Asp Arg Gly Gln Gln Leu Gln Gln Lys Gln Gln
35 40 45

Asp Leu Glu Gln Glu Gly Leu Glu Ala Thr Gln Gly Leu Leu Ala Gly
50 55 60

Glu Trp Ala Pro Pro Leu Trp Xaa Leu Gly Ser Leu Phe Gln Ala Phe
65 70 75 80

Val Lys Arg Glu Ser Gln Ala Tyr Ala
85

<210> 371
<211> 508
<212> PRT
<213> Homo sapiens

<400> 371
Met Asp Pro Lys Leu Gly Arg Met Ala Ala Ser Leu Leu Ala Val Leu
1 5 10 15

Leu Leu Leu Leu Leu Glu Arg Gly Met Phe Ser Ser Pro Ser Pro Pro
20 25 30

Pro Ala Leu Leu Glu Lys Val Phe Gln Tyr Ile Asp Leu His Gln Asp
35 40 45

```
Glu Phe Val Gln Thr Leu Lys Glu Trp Val Ala Ile Glu Ser Asp Ser
    50                  55                  60

Val Gln Pro Val Pro Arg Phe Arg Gln Glu Leu Phe Arg Met Met Ala
65                  70                  75                  80

Val Ala Ala Asp Thr Leu Gln Arg Leu Gly Ala Arg Val Ala Ser Val
                85                  90                  95

Asp Met Gly Pro Gln Gln Leu Pro Asp Gly Gln Ser Leu Pro Ile Pro
            100                 105                 110

Pro Val Ile Leu Ala Glu Leu Gly Ser Asp Pro Thr Lys Gly Thr Val
        115                 120                 125

Cys Phe Tyr Gly His Leu Asp Val Gln Pro Ala Asp Arg Gly Asp Gly
    130                 135                 140

Trp Leu Thr Asp Pro Tyr Val Leu Thr Glu Val Asp Gly Lys Leu Tyr
145                 150                 155                 160

Gly Arg Gly Ala Thr Asp Asn Lys Gly Pro Val Leu Ala Trp Ile Asn
                165                 170                 175

Ala Val Ser Ala Phe Arg Ala Leu Glu Gln Asp Leu Pro Val Asn Ile
            180                 185                 190

Lys Phe Ile Ile Glu Gly Met Glu Glu Ala Gly Ser Val Ala Leu Glu
        195                 200                 205

Glu Leu Val Glu Lys Glu Lys Asp Arg Phe Phe Ser Gly Val Asp Tyr
    210                 215                 220

Ile Val Ile Ser Asp Asn Leu Trp Ile Ser Gln Arg Lys Pro Ala Ile
225                 230                 235                 240

Thr Tyr Gly Thr Arg Gly Asn Ser Tyr Phe Met Val Glu Val Lys Cys
                245                 250                 255

Arg Asp Gln Asp Phe His Ser Gly Thr Phe Gly Gly Ile Leu His Glu
            260                 265                 270

Pro Met Ala Asp Leu Val Ala Leu Leu Gly Ser Leu Val Asp Ser Ser
        275                 280                 285

Gly His Ile Leu Val Pro Gly Ile Tyr Asp Glu Val Val Pro Leu Thr
    290                 295                 300

Glu Glu Glu Ile Asn Thr Tyr Lys Ala Ile His Leu Asp Leu Glu Glu
305                 310                 315                 320

Tyr Arg Asn Ser Ser Arg Val Glu Lys Phe Leu Phe Asp Thr Lys Glu
                325                 330                 335

Glu Ile Leu Met His Leu Trp Arg Tyr Pro Ser Leu Ser Ile His Gly
            340                 345                 350

Ile Glu Gly Ala Phe Asp Glu Pro Gly Thr Lys Thr Val Ile Pro Gly
        355                 360                 365

Arg Val Ile Gly Lys Phe Ser Ile Arg Leu Val Pro His Met Asn Val
```

370 375 380

Ser Ala Val Glu Lys Gln Val Thr Arg His Leu Glu Asp Val Phe Ser
385 390 395 400

Lys Arg Asn Ser Ser Asn Lys Met Val Val Ser Met Thr Leu Gly Leu
405 410 415

His Pro Trp Ile Ala Asn Ile Asp Asp Thr Gln Tyr Leu Ala Ala Lys
420 425 430

Arg Ala Ile Arg Thr Val Phe Gly Thr Glu Pro Asp Met Ile Arg Asp
435 440 445

Gly Ser Thr Ile Pro Ile Ala Lys Met Phe Gln Glu Ile Val His Lys
450 455 460

Ser Val Val Leu Ile Pro Leu Gly Ala Val Asp Asp Gly Glu His Ser
465 470 475 480

Gln Asn Glu Lys Ile Asn Arg Trp Asn Tyr Ile Glu Gly Thr Lys Leu
485 490 495

Phe Ala Ala Phe Phe Leu Glu Met Ala Gln Leu His
500 505

<210> 372
<211> 77
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (69)
<223> Xaa equals any amino acid

<400> 372
Met Thr Gly Gln Ile Pro Arg Leu Ser Lys Val Asn Leu Phe Thr Leu
1 5 10 15

Leu Ser Leu Trp Met Glu Leu Phe Pro Ala Glu Ala Gln Arg Gln Lys
20 25 30

Ser Gln Lys Asn Glu Glu Gly Lys His Gly Pro Leu Gly Asp Asn Glu
35 40 45

Glu Arg Thr Arg Val Ser Thr Asp Lys Arg Gln Asp Tyr Trp Glu Gln
50 55 60

Leu Arg Cys Leu Xaa Glu Arg Phe Thr Ile Thr Ala Gly
65 70 75

<210> 373
<211> 44
<212> PRT
<213> Homo sapiens

<400> 373
Met Arg Leu Arg Asn Gly Thr Val Ala Thr Ala Leu Ala Phe Ile Thr
1 5 10 15

Ser Phe Leu Thr Leu Ser Trp Tyr Thr Thr Trp Gln Asn Gly Lys Gly
20 25 30

Lys Glu Asn Asp Ser Glu Asn Val His Glu Met Tyr
35 40

<210> 374
<211> 327
<212> PRT
<213> Homo sapiens

<400> 374
Met Ala Cys Arg Lys Leu Ala Val Ala His Pro Leu Leu Leu Leu Arg
1 5 10 15

His Leu Pro Met Ile Ala Ala Leu Leu His Gly Arg Thr His Leu Asn
20 25 30

Phe Gln Glu Phe Arg Gln Gln Asn His Leu Ser Cys Phe Leu His Val
35 40 45

Leu Gly Leu Leu Glu Leu Leu Gln Pro His Val Phe Arg Ser Glu His
50 55 60

Gln Gly Ala Leu Trp Asp Cys Leu Leu Ser Phe Ile Arg Leu Leu Leu
65 70 75 80

Asn Tyr Arg Lys Ser Ser Arg His Leu Ala Ala Phe Ile Asn Lys Phe
85 90 95

Val Gln Phe Ile His Lys Tyr Ile Thr Tyr Asn Ala Pro Ala Ala Ile
100 105 110

Ser Phe Leu Gln Lys His Ala Asp Pro Leu His Asp Leu Ser Phe Asp
115 120 125

Asn Ser Asp Leu Val Met Leu Lys Ser Leu Leu Ala Gly Leu Ser Leu
130 135 140

Pro Ser Arg Asp Asp Arg Thr Asp Arg Gly Leu Asp Glu Glu Gly Glu
145 150 155 160

Glu Glu Ser Ser Ala Gly Ser Leu Pro Leu Val Ser Val Ser Leu Phe
165 170 175

Thr Pro Leu Thr Ala Ala Glu Met Ala Pro Tyr Met Lys Arg Leu Ser
180 185 190

Arg Gly Gln Thr Val Glu Asp Leu Leu Glu Val Leu Ser Asp Ile Asp
195 200 205

Glu Met Ser Arg Arg Arg Pro Glu Ile Leu Ser Phe Phe Ser Thr Asn
210 215 220

Leu Gln Arg Leu Met Ser Ser Ala Glu Glu Cys Cys Arg Asn Leu Ala

225 230 235 240

Phe Ser Leu Ala Leu Arg Ser Met Gln Asn Ser Pro Ser Ile Ala Ala
245 250 255

Ala Phe Leu Pro Thr Phe Met Tyr Cys Leu Gly Ser Gln Asp Phe Glu
260 265 270

Val Val Gln Thr Ala Leu Arg Asn Leu Pro Glu Tyr Ala Leu Leu Cys
275 280 285

Gln Glu His Ala Ala Val Leu Leu His Arg Ala Phe Leu Val Gly Met
290 295 300

Tyr Gly Gln Met Asp Pro Ser Ala Gln Ile Ser Glu Ala Leu Arg Ile
305 310 315 320

Leu His Met Glu Ala Val Met
325

<210> 375
<211> 91
<212> PRT
<213> Homo sapiens

<400> 375
Met Gly Asp Lys Leu Gly Met Ala Arg Ala Pro Ser Val Ala Leu Ala
1 5 10 15

Gln Leu Trp Leu Ile Cys Leu Cys Pro Glu Ser Leu Ala Ser Phe Val
20 25 30

Gln Ala Val Pro Trp Lys Val Leu Gln Pro Ser Ser Asn Arg Ser Thr
35 40 45

Asp Cys Ser Pro His Met Arg Pro Thr Cys Glu Thr Leu Gly Ser Arg
50 55 60

Lys Ala Gln Asp Leu Val Leu Asp Thr Met Cys Leu Ser Thr Asp Asp
65 70 75 80

Cys Gln Gly Leu Ile Cys Arg Gly His Arg Ser
85 90

<210> 376
<211> 243
<212> PRT
<213> Homo sapiens

<400> 376
Met Gly Thr Leu Pro Trp Leu Leu Ala Phe Phe Ile Leu Gly Leu Gln
1 5 10 15

Ala Trp Asp Thr Pro Thr Ile Val Ser Arg Lys Glu Trp Gly Ala Arg
20 25 30

Pro Leu Ala Cys Arg Ala Leu Leu Thr Leu Pro Val Ala Tyr Ile Ile

35 40 45

Thr Asp Gln Leu Pro Gly Met Gln Cys Gln Gln Gln Ser Val Cys Ser
50 55 60

Gln Met Leu Arg Gly Leu Gln Ser His Ser Val Tyr Thr Ile Gly Trp
65 70 75 80

Cys Asp Val Ala Tyr Asn Phe Leu Val Gly Asp Asp Gly Arg Val Tyr
85 90 95

Glu Gly Val Gly Trp Asn Ile Gln Gly Leu His Thr Gln Gly Tyr Asn
100 105 110

Asn Ile Ser Leu Gly Ile Ala Phe Phe Gly Asn Lys Ile Ser Ser Ser
115 120 125

Pro Ser Pro Ala Ala Leu Ser Ala Ala Glu Gly Leu Ile Ser Tyr Ala
130 135 140

Ile Gln Lys Gly His Leu Ser Pro Arg Tyr Ile Gln Pro Leu Leu Leu
145 150 155 160

Lys Glu Glu Thr Cys Leu Asp Pro Gln His Pro Val Met Pro Arg Lys
165 170 175

Val Cys Pro Asn Ile Ile Lys Arg Ser Ala Trp Glu Ala Arg Glu Thr
180 185 190

His Cys Pro Lys Met Asn Leu Pro Ala Lys Tyr Val Ile Ile Ile His
195 200 205

Thr Ala Gly Thr Ser Cys Thr Val Ser Thr Asp Cys Gln Thr Val Val
210 215 220

Arg Asn Ile Gln Ser Phe His Met Asp Thr Arg Asn Phe Cys Asp Ile
225 230 235 240

Gly Tyr Gln

<210> 377
<211> 80
<212> PRT
<213> Homo sapiens

<400> 377
Met Lys Leu Ser Gly Met Phe Leu Leu Leu Ser Leu Ala Leu Phe Cys
1 5 10 15

Phe Leu Thr Gly Val Phe Ser Gln Gly Gly Gln Val Asp Cys Gly Glu
20 25 30

Phe Gln Asp Thr Lys Val Tyr Cys Thr Arg Glu Ser Asn Pro His Cys
35 40 45

Gly Ser Asp Gly Gln Thr Tyr Gly Asn Lys Cys Ala Phe Cys Lys Ala
50 55 60

Ile Val Lys Ser Gly Gly Lys Ile Ser Leu Lys His Pro Gly Lys Cys
65 70 75 80

<210> 378
<211> 301
<212> PRT
<213> Homo sapiens

<400> 378
Met Ala Arg His Gly Leu Pro Leu Leu Pro Leu Leu Ser Leu Leu Val
1 5 10 15

Gly Ala Trp Leu Lys Leu Gly Asn Gly Gln Ala Thr Ser Met Val Gln
20 25 30

Leu Gln Gly Gly Arg Phe Leu Met Gly Thr Asn Ser Pro Asp Ser Arg
35 40 45

Asp Gly Glu Gly Pro Val Arg Glu Ala Thr Val Lys Pro Phe Ala Ile
50 55 60

Asp Ile Phe Pro Val Thr Asn Lys Asp Phe Arg Asp Phe Val Arg Glu
65 70 75 80

Lys Lys Tyr Arg Thr Glu Ala Glu Met Phe Gly Trp Ser Phe Val Phe
85 90 95

Glu Asp Phe Val Ser Asp Glu Leu Arg Asn Lys Ala Thr Gln Pro Met
100 105 110

Lys Ser Val Leu Trp Trp Leu Pro Val Glu Lys Ala Phe Trp Arg Gln
115 120 125

Pro Ala Gly Pro Gly Ser Gly Ile Arg Glu Arg Leu Glu His Pro Val
130 135 140

Leu His Val Ser Trp Asn Asp Ala Arg Ala Tyr Cys Ala Trp Arg Gly
145 150 155 160

Lys Arg Leu Pro Thr Glu Glu Glu Trp Glu Phe Ala Ala Arg Gly Gly
165 170 175

Leu Lys Gly Gln Val Tyr Pro Trp Gly Asn Trp Phe Gln Pro Asn Arg
180 185 190

Thr Asn Leu Trp Gln Gly Lys Phe Pro Lys Gly Asp Lys Ala Glu Asp
195 200 205

Gly Phe His Gly Val Ser Pro Val Asn Ala Phe Pro Ala Gln Asn Asn
210 215 220

Tyr Gly Leu Tyr Asp Leu Leu Gly Asn Val Trp Glu Trp Thr Ala Ser
225 230 235 240

Pro Tyr Gln Ala Ala Glu Gln Asp Met Arg Val Leu Arg Gly Ala Ser
245 250 255

```
Trp Ile Asp Thr Ala Asp Gly Ser Ala Asn His Arg Ala Arg Val Thr
            260                 265                 270

Thr Arg Met Gly Asn Thr Pro Asp Ser Ala Ser Asp Asn Leu Gly Phe
        275                 280                 285

Arg Cys Ala Ala Asp Ala Gly Arg Pro Pro Gly Glu Leu
    290                 295                 300



<210> 379
<211> 438
<212> PRT
<213> Homo sapiens

<400> 379
Met Pro Cys Thr Cys Thr Trp Arg Asn Trp Arg Gln Trp Ile Arg Pro
  1               5                  10                  15

Leu Val Ala Val Ile Tyr Leu Val Ser Ile Val Val Ala Val Pro Leu
             20                  25                  30

Cys Val Trp Glu Leu Gln Lys Leu Glu Val Gly Ile His Thr Lys Ala
         35                  40                  45

Trp Phe Ile Ala Gly Ile Phe Leu Leu Leu Thr Ile Pro Ile Ser Leu
     50                  55                  60

Trp Val Ile Leu Gln His Leu Val His Tyr Thr Gln Pro Glu Leu Gln
 65                  70                  75                  80

Lys Pro Ile Ile Arg Ile Leu Trp Met Val Pro Ile Tyr Ser Leu Asp
                 85                  90                  95

Ser Trp Ile Ala Leu Lys Tyr Pro Gly Ile Ala Ile Tyr Val Asp Thr
            100                 105                 110

Cys Arg Glu Cys Tyr Glu Ala Tyr Val Ile Tyr Asn Phe Met Gly Phe
        115                 120                 125

Leu Thr Asn Tyr Leu Thr Asn Arg Tyr Pro Asn Leu Val Leu Ile Leu
    130                 135                 140

Glu Ala Lys Asp Gln Gln Lys His Phe Pro Pro Leu Cys Cys Cys Pro
145                 150                 155                 160

Pro Trp Ala Met Gly Glu Val Leu Leu Phe Arg Cys Lys Leu Gly Val
                165                 170                 175

Leu Gln Tyr Thr Val Val Arg Pro Phe Thr Thr Ile Val Ala Leu Ile
            180                 185                 190

Cys Glu Leu Leu Gly Ile Tyr Asp Glu Gly Asn Phe Ser Phe Ser Asn
        195                 200                 205

Ala Trp Thr Tyr Leu Val Ile Ile Asn Asn Met Ser Gln Leu Phe Ala
    210                 215                 220

Met Tyr Cys Leu Leu Leu Phe Tyr Lys Val Leu Lys Glu Glu Leu Ser
```

225 230 235 240

Pro Ile Gln Pro Val Gly Lys Phe Leu Cys Val Lys Leu Val Val Phe
245 250 255

Val Ser Phe Trp Gln Ala Val Val Ile Ala Leu Leu Val Lys Val Gly
260 265 270

Val Ile Ser Glu Lys His Thr Trp Glu Trp Gln Thr Val Glu Ala Val
275 280 285

Ala Thr Gly Leu Gln Asp Phe Ile Ile Cys Ile Glu Met Phe Leu Ala
290 295 300

Ala Ile Ala His His Tyr Thr Phe Ser Tyr Lys Pro Tyr Val Gln Glu
305 310 315 320

Ala Glu Glu Gly Ser Cys Phe Asp Ser Phe Leu Ala Met Trp Asp Val
325 330 335

Ser Asp Ile Arg Asp Asp Ile Ser Glu Gln Val Arg His Val Gly Arg
340 345 350

Thr Val Arg Gly His Pro Arg Lys Lys Leu Phe Pro Glu Asp Gln Asp
355 360 365

Gln Asn Glu His Thr Ser Leu Leu Ser Ser Ser Ser Gln Asp Ala Ile
370 375 380

Ser Ile Ala Ser Ser Met Pro Pro Ser Pro Met Gly His Tyr Gln Gly
385 390 395 400

Phe Gly His Thr Val Thr Pro Gln Thr Thr Pro Thr Thr Ala Lys Ile
405 410 415

Ser Asp Glu Ile Leu Ser Asp Thr Ile Gly Glu Lys Lys Glu Pro Ser
420 425 430

Asp Lys Ser Val Asp Ser
435

<210> 380
<211> 107
<212> PRT
<213> Homo sapiens

<400> 380
Met Val Arg Tyr Thr Tyr Ser Met Leu Ser Val Ile Gly Ile Ser Tyr
1 5 10 15

Ala Val Leu Thr Trp Leu Ser Gln Thr Leu Trp Met Pro Ile Tyr Pro
20 25 30

Leu Cys Val Leu Ala Glu Ala Phe Ala Ile Tyr Gln Ser Leu Pro Tyr
35 40 45

Phe Glu Ser Phe Gly Thr Tyr Ser Thr Lys Leu Pro Phe Asp Leu Ser
50 55 60

```
Ile Tyr Phe Pro Tyr Val Leu Lys Ile Tyr Leu Met Met Leu Phe Ile
 65                  70                  75                  80

Gly Met Tyr Phe Thr Tyr Ser His Leu Tyr Ser Glu Arg Arg Asp Ile
                 85                  90                  95

Leu Gly Ile Phe Pro Ile Lys Lys Lys Lys Met
            100                 105
```

<210> 381
<211> 234
<212> PRT
<213> Homo sapiens

<400> 381

```
Met Arg Ile Arg Phe Thr Ser Pro His Pro Lys Asp Phe Pro Asp Glu
  1               5                  10                  15

Val Leu Gln Leu Ile His Glu Arg Asp Asn Ile Cys Lys Gln Ile His
             20                  25                  30

Leu Pro Ala Gln Ser Gly Ser Ser Arg Val Leu Glu Ala Met Arg Arg
         35                  40                  45

Gly Tyr Ser Arg Glu Ala Tyr Val Glu Leu Val His His Ile Arg Glu
     50                  55                  60

Ser Ile Pro Gly Val Ser Leu Ser Ser Asp Phe Ile Ala Gly Phe Cys
 65                  70                  75                  80

Gly Glu Thr Glu Glu Asp His Val Gln Thr Val Ser Leu Leu Arg Glu
                 85                  90                  95

Val Gln Tyr Asn Met Gly Phe Leu Phe Ala Tyr Ser Met Arg Gln Lys
            100                 105                 110

Thr Arg Ala Tyr His Arg Leu Lys Asp Asp Val Pro Glu Glu Val Lys
        115                 120                 125

Leu Arg Arg Leu Glu Glu Leu Ile Thr Ile Phe Arg Glu Glu Ala Thr
    130                 135                 140

Lys Ala Asn Gln Thr Ser Val Gly Cys Thr Gln Leu Val Leu Val Glu
145                 150                 155                 160

Gly Leu Ser Lys Arg Ser Ala Thr Asp Leu Cys Gly Arg Asn Asp Gly
                165                 170                 175

Asn Leu Lys Val Ile Phe Pro Asp Ala Glu Met Glu Asp Val Asn Asn
            180                 185                 190

Pro Gly Leu Arg Val Arg Ala Gln Pro Gly Asp Tyr Val Leu Val Lys
        195                 200                 205

Ile Thr Ser Ala Ser Ser Gln Thr Leu Arg Gly His Val Leu Cys Arg
    210                 215                 220

Thr Thr Leu Arg Asp Ser Ser Ala Tyr Cys
225                 230
```

<210> 382
<211> 470
<212> PRT
<213> Homo sapiens

<400> 382
Met Trp Phe Thr Tyr Leu Leu Leu Tyr Leu His Ser Val Arg Ala Tyr
1 5 10 15

Ser Ser Arg Gly Ala Gly Leu Leu Leu Leu Leu Gly Gln Val Ala Asp
20 25 30

Gly Leu Cys Thr Pro Leu Val Gly Tyr Glu Ala Asp Arg Ala Ala Ser
35 40 45

Cys Cys Ala Arg Tyr Gly Pro Arg Lys Ala Trp His Leu Val Gly Thr
50 55 60

Val Cys Val Leu Leu Ser Phe Pro Phe Ile Phe Ser Pro Cys Leu Gly
65 70 75 80

Cys Gly Ala Ala Thr Pro Glu Trp Ala Ala Leu Leu Tyr Tyr Gly Pro
85 90 95

Phe Ile Val Ile Phe Gln Phe Gly Trp Ala Ser Thr Gln Ile Ser His
100 105 110

Leu Ser Leu Ile Pro Glu Leu Val Thr Asn Asp His Glu Lys Val Glu
115 120 125

Leu Thr Ala Leu Arg Tyr Ala Phe Thr Val Val Ala Asn Ile Thr Val
130 135 140

Tyr Gly Ala Ala Trp Leu Leu Leu His Leu Gln Gly Ser Ser Arg Val
145 150 155 160

Glu Pro Thr Gln Asp Ile Ser Ile Ser Asp Gln Leu Gly Gly Gln Asp
165 170 175

Val Pro Val Phe Arg Asn Leu Ser Leu Leu Val Val Gly Val Gly Ala
180 185 190

Val Phe Ser Leu Leu Phe His Leu Gly Thr Arg Glu Arg Arg Arg Pro
195 200 205

His Ala Glu Glu Pro Gly Glu His Thr Pro Leu Leu Ala Pro Ala Thr
210 215 220

Ala Gln Pro Leu Leu Leu Trp Lys His Trp Leu Arg Glu Pro Ala Phe
225 230 235 240

Tyr Gln Val Gly Ile Leu Tyr Met Thr Thr Arg Leu Ile Val Asn Leu
245 250 255

Ser Gln Thr Tyr Met Ala Met Tyr Leu Thr Tyr Ser Leu His Leu Pro
260 265 270

Lys Lys Phe Ile Ala Thr Ile Pro Leu Val Met Tyr Leu Ser Gly Phe

275 280 285

Leu Ser Ser Phe Leu Met Lys Pro Ile Asn Lys Cys Ile Gly Arg Asn
290 295 300

Met Thr Tyr Phe Ser Gly Leu Leu Val Ile Leu Ala Phe Ala Ala Trp
305 310 315 320

Val Ala Leu Ala Glu Gly Leu Gly Val Ala Val Tyr Ala Ala Ala Val
325 330 335

Leu Leu Gly Ala Gly Cys Ala Thr Ile Leu Val Thr Ser Leu Ala Met
340 345 350

Thr Ala Asp Leu Ile Gly Pro His Thr Asn Ser Gly Ala Phe Val Tyr
355 360 365

Gly Ser Met Ser Phe Leu Asp Lys Val Ala Asn Gly Leu Ala Val Met
370 375 380

Ala Ile Gln Ser Leu His Pro Cys Pro Ser Glu Leu Cys Cys Arg Ala
385 390 395 400

Cys Val Ser Phe Tyr His Trp Ala Met Val Ala Val Thr Gly Gly Val
405 410 415

Gly Val Ala Ala Ala Leu Cys Leu Cys Ser Leu Leu Leu Trp Pro Thr
420 425 430

Arg Leu Arg Arg Ser Arg Gly Gly Glu His Arg Thr Pro Ser Glu Gly
435 440 445

Glu Gly Ile Ser Thr Ala Pro Pro Pro Cys Trp Asn Glu Thr Gln Pro
450 455 460

Gln Gly Gly Ala Lys Leu
465 470

<210> 383
<211> 260
<212> PRT
<213> Homo sapiens

<400> 383
Met Ala Gly Ser Pro Leu Leu Trp Gly Pro Arg Ala Gly Gly Val Gly
1 5 10 15

Leu Leu Val Leu Leu Leu Leu Gly Leu Phe Arg Pro Pro Pro Ala Leu
20 25 30

Cys Ala Arg Pro Val Lys Glu Pro Arg Gly Leu Ser Ala Ala Ser Pro
35 40 45

Pro Leu Ala Glu Thr Gly Ala Pro Arg Arg Phe Arg Arg Ser Val Pro
50 55 60

Arg Gly Glu Ala Ala Gly Ala Val Gln Asp Leu Ala Arg Ala Leu Ala
65 70 75 80

His Leu Leu Glu Ala Glu Arg Gln Glu Arg Ala Arg Ala Glu Ala Gln
85 90 95

Glu Ala Glu Asp Gln Gln Ala Arg Val Leu Ala Gln Leu Leu Arg Val
100 105 110

Trp Gly Ala Pro Arg Asn Ser Asp Pro Ala Leu Gly Leu Asp Asp Asp
115 120 125

Pro Asp Ala Pro Ala Ala Gln Leu Ala Arg Ala Leu Leu Arg Ala Arg
130 135 140

Leu Asp Pro Ala Ala Leu Ala Ala Gln Leu Val Pro Ala Pro Val Pro
145 150 155 160

Ala Ala Ala Leu Arg Pro Arg Pro Pro Val Tyr Asp Asp Gly Pro Ala
165 170 175

Gly Pro Asp Ala Glu Glu Ala Gly Asp Glu Thr Pro Asp Val Asp Pro
180 185 190

Glu Leu Leu Arg Tyr Leu Leu Gly Arg Ile Leu Ala Gly Ser Ala Asp
195 200 205

Ser Glu Gly Val Ala Ala Pro Arg Arg Leu Arg Arg Ala Ala Asp His
210 215 220

Asp Val Gly Ser Glu Leu Pro Pro Glu Gly Val Leu Gly Ala Leu Leu
225 230 235 240

Arg Val Lys Arg Leu Glu Thr Pro Ala Pro Gln Val Pro Ala Arg Arg
245 250 255

Leu Leu Pro Pro
260

<210> 384
<211> 95
<212> PRT
<213> Homo sapiens

<400> 384
Met His Leu Cys Ile Cys Ala Val Trp Val Leu Val Ala Leu Leu Arg
1 5 10 15

Met His Gly Ala Ser Pro Ala Gln Thr Ser Gly Thr Arg Ser Gly Asn
20 25 30

Gly Gly Cys Arg Arg His Gly Ala Gly Gln Gly Arg Gly Ala Ala Thr
35 40 45

Gln Pro Leu Arg Pro Pro Arg Gly Thr Ala Ser Gly Gln Leu Met Ala
50 55 60

Leu Leu Ser Ala Leu Leu Pro Arg Leu Ser Gly Ser Ser Thr Pro Met
65 70 75 80

Met Ala His Gly Arg Pro Ala Pro Pro Gln Trp Ser Arg Val Ser
85 90 95

<210> 385
<211> 130
<212> PRT
<213> Homo sapiens

<400> 385
Met Glu Thr Leu Gly Ala Leu Leu Val Leu Glu Phe Leu Leu Leu Ser
1 5 10 15

Pro Val Glu Ala Gln Gln Ala Thr Glu His Arg Leu Lys Pro Trp Leu
20 25 30

Val Gly Leu Ala Ala Val Val Gly Phe Leu Phe Ile Val Tyr Leu Val
35 40 45

Leu Leu Ala Asn Arg Leu Trp Cys Ser Lys Ala Arg Ala Glu Asp Glu
50 55 60

Glu Glu Thr Thr Phe Arg Met Glu Ser Asn Leu Tyr Gln Asp Gln Ser
65 70 75 80

Glu Asp Lys Arg Glu Lys Lys Glu Ala Lys Glu Lys Glu Glu Lys Arg
85 90 95

Lys Lys Glu Lys Lys Thr Ala Lys Glu Gly Glu Ser Asn Leu Gly Leu
100 105 110

Asp Leu Glu Glu Lys Glu Pro Gly Asp His Glu Arg Ala Lys Ser Thr
115 120 125

Val Met
130

<210> 386
<211> 41
<212> PRT
<213> Homo sapiens

<400> 386
Met Asn Leu Ser Phe Leu Ser Phe Phe Leu Phe Phe Tyr Leu Leu Trp
1 5 10 15

Ser Pro Ala Glu Ser Val Tyr Lys Lys Gly Met Val Lys Lys Asn Leu
20 25 30

Ser His Ser Ile Val Glu Lys Ile Lys
35 40

<210> 387
<211> 113
<212> PRT
<213> Homo sapiens

<220>

<221> SITE
<222> (38)
<223> Xaa equals any amino acid

<400> 387
Met Arg Pro Leu Leu Leu Gly Gly Tyr Trp Val Leu Cys Leu Ser Val
1 5 10 15

Leu Gly His Ala Ala Leu Tyr His Phe Trp Leu Arg Glu Glu Gly Lys
20 25 30

Gly Pro Pro Gln Val Xaa Ser Val Leu Ala Leu Ala Leu Pro Ala Gly
35 40 45

Ser Cys Ala Pro Gly Leu Pro Phe Pro Gly Pro Leu Ile Pro Thr Gln
50 55 60

Leu Leu Phe Ala Leu Glu Trp Gly Thr Pro Thr Pro Leu Arg Asp His
65 70 75 80

Pro Pro His Ser Met His Ser Ala Pro Gln Asn Pro Pro Val Phe Leu
85 90 95

Gly Thr His Thr Cys Pro Pro Ser Trp Tyr Phe Arg Leu Ile Pro Gln
100 105 110

Ala

<210> 388
<211> 161
<212> PRT
<213> Homo sapiens

<400> 388
Met Ala Leu Ser Leu Thr Leu Cys Phe Val Met Phe Trp Thr Pro Asn
1 5 10 15

Val Ser Glu Lys Ile Leu Ile Asp Ile Ile Gly Val Asp Phe Ala Phe
20 25 30

Ala Glu Leu Cys Val Val Pro Leu Arg Ile Phe Ser Phe Phe Pro Val
35 40 45

Pro Val Thr Val Arg Ala His Leu Thr Gly Trp Leu Met Thr Leu Lys
50 55 60

Lys Thr Phe Val Leu Ala Pro Ser Ser Val Leu Arg Ile Ile Val Leu
65 70 75 80

Ile Ala Ser Leu Val Val Leu Pro Tyr Leu Gly Val His Gly Ala Thr
85 90 95

Leu Gly Val Gly Ser Leu Leu Ala Gly Phe Val Gly Glu Ser Thr Met
100 105 110

Val Ala Ile Ala Ala Cys Tyr Val Tyr Arg Lys Gln Lys Lys Lys Met
115 120 125

Glu Asn Glu Ser Ala Thr Glu Gly Glu Asp Ser Ala Met Thr Asp Met
    130   135   140

Pro Pro Thr Glu Glu Val Thr Asp Ile Val Glu Met Arg Glu Glu Asn
145   150   155   160

Glu

<210> 389
<211> 348
<212> PRT
<213> Homo sapiens

<400> 389
Met Asn Met Thr Gln Ala Arg Val Leu Val Ala Ala Val Val Gly Leu
1   5   10   15

Val Ala Val Leu Leu Tyr Ala Ser Ile His Lys Ile Glu Glu Gly His
            20   25   30

Leu Ala Val Tyr Tyr Arg Gly Gly Ala Leu Leu Thr Ser Pro Ser Gly
        35   40   45

Pro Gly Tyr His Ile Met Leu Pro Phe Ile Thr Thr Phe Arg Ser Val
    50   55   60

Gln Thr Thr Leu Gln Thr Asp Glu Val Lys Asn Val Pro Cys Gly Thr
65   70   75   80

Ser Gly Gly Val Met Ile Tyr Ile Asp Arg Ile Glu Val Val Asn Met
                85   90   95

Leu Ala Pro Tyr Ala Val Phe Asp Ile Val Arg Asn Tyr Thr Ala Asp
            100   105   110

Tyr Asp Lys Thr Leu Ile Phe Asn Lys Ile His His Glu Leu Asn Gln
        115   120   125

Phe Cys Ser Ala His Thr Leu Gln Glu Val Tyr Ile Glu Leu Phe Asp
    130   135   140

Gln Ile Asp Glu Asn Leu Lys Gln Ala Leu Gln Lys Asp Leu Asn Leu
145   150   155   160

Met Ala Pro Gly Leu Thr Ile Gln Ala Val Arg Val Thr Lys Pro Lys
                165   170   175

Ile Pro Glu Ala Ile Arg Arg Asn Phe Glu Leu Met Glu Ala Glu Lys
            180   185   190

Thr Lys Leu Leu Ile Ala Ala Gln Lys Gln Lys Val Val Glu Lys Glu
        195   200   205

Ala Glu Thr Glu Arg Lys Lys Ala Val Ile Glu Ala Glu Lys Ile Ala
    210   215   220

Gln Val Ala Lys Ile Arg Phe Gln Gln Lys Val Met Glu Lys Glu Thr
225   230   235   240

```
Glu Lys Arg Ile Ser Glu Ile Glu Asp Ala Ala Phe Leu Ala Arg Glu
                245                 250                 255

Lys Ala Lys Ala Asp Ala Glu Tyr Tyr Ala Ala His Lys Tyr Ala Thr
            260                 265                 270

Ser Asn Lys His Lys Leu Thr Pro Glu Tyr Leu Glu Leu Lys Lys Tyr
        275                 280                 285

Gln Ala Ile Ala Ser Asn Ser Lys Ile Tyr Phe Gly Ser Asn Ile Pro
    290                 295                 300

Asn Met Phe Val Asp Ser Ser Cys Ala Leu Lys Tyr Ser Asp Ile Arg
305                 310                 315                 320

Thr Gly Arg Glu Ser Ser Leu Pro Ser Lys Glu Ala Leu Glu Pro Ser
                325                 330                 335

Gly Glu Asn Val Ile Gln Asn Lys Glu Ser Thr Gly
            340                 345



<210> 390
<211> 44
<212> PRT
<213> Homo sapiens

<400> 390
Met Pro Leu Cys Gly Leu Tyr Cys Leu Arg Ile Leu Met Phe Pro Leu
  1               5                  10                  15

Arg Ser Ala Asn Ser Val Pro Leu Gln Cys Leu Pro Pro Ser Ser Leu
             20                  25                  30

Ala Asn Lys Asp Ser His Phe Arg Ala Pro Arg Lys
         35                  40



<210> 391
<211> 50
<212> PRT
<213> Homo sapiens

<400> 391
Met Pro Gly Ile Leu Ala Gly Ile Pro Val Lys Asp Leu Cys Leu Ser
  1               5                  10                  15

Leu Leu Gln Gly Phe Arg Leu Leu Leu Leu Cys Val Cys Pro Gly Trp
             20                  25                  30

Leu Ser Gly Trp Met Gly Gly Gln Lys Gly Ser Pro Arg Ile Val Asp
         35                  40                  45

Ile Gly
     50
```

<210> 392
<211> 206
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (143)
<223> Xaa equals any amino acid

<400> 392

```
Met Ala Ser His Gly Leu Cys Pro Cys Leu Leu Met Gly Thr Gly Trp
 1               5                  10                  15

Gly Leu Trp Thr Leu Leu Pro Asp Leu Glu Val Met Ala Gly Lys Gly
            20                  25                  30

Arg Met Pro Phe Ala Gly Ile Ser Val Thr Ser Gly Phe Leu Arg Ser
        35                  40                  45

Leu Lys Arg Ala Pro Leu Pro His Thr Gly Ser Pro Asp Pro Arg Pro
    50                  55                  60

Ser Gly Ile Trp Ser Gly Val Arg Thr Thr Ser Glu Glu Ala Gly Ala
65                  70                  75                  80

Thr Ser Thr Gln Ile Ser Thr Ala Ala Pro Arg Phe His Ser Arg Arg
                85                  90                  95

Lys Gly Pro Lys Arg Asn Leu Ala Pro Gln Leu Arg Val Leu Val His
            100                 105                 110

Arg Thr Val Pro Pro Gly Gln Leu Val Tyr Ala Pro Gln Thr Val Asp
        115                 120                 125

Ser Leu Arg Gly Thr Leu Leu Arg Pro Pro Ala Trp Leu Leu Xaa Gln
    130                 135                 140

Val Pro Cys Phe Tyr Ser Gly Gln Pro Leu Leu Val Ser Ala Ser Val
145                 150                 155                 160

Leu Cys Arg Asp Leu Met Gln Phe Leu Phe Leu Leu Lys Ser Tyr Leu
                165                 170                 175

Leu Pro Phe Leu Glu Val Cys Arg Ile Gly Trp Glu Gln Ile Gln Arg
            180                 185                 190

Ile Leu Gly Ala Gly Leu Trp Arg Gln Lys Glu Gly Asn Gly
        195                 200                 205
```

<210> 393
<211> 75
<212> PRT
<213> Homo sapiens

<400> 393

```
Met Ser Arg Phe Ile Leu Asn His Leu Val Leu Ala Ile Pro Leu Arg
 1               5                  10                  15
```

Val Leu Val Val Leu Trp Ala Phe Val Leu Gly Leu Ser Arg Val Met
20 25 30

Leu Gly Arg His Asn Val Thr Asp Val Ala Phe Gly Phe Phe Leu Gly
35 40 45

Tyr Met Gln Tyr Ser Ile Val Asp Tyr Cys Trp Leu Ser Pro His Asn
50 55 60

Ala Pro Val Leu Phe Leu Leu Trp Ser Gln Arg
65 70 75

<210> 394
<211> 97
<212> PRT
<213> Homo sapiens

<400> 394
Met Cys Lys Gly Leu Lys Asn Pro Glu Gly Leu Leu Leu Leu Leu Leu
1 5 10 15

Leu Leu Leu Phe Thr Asp Thr Ser Asn Ser His Cys Leu Pro Pro Tyr
20 25 30

Leu Ser Cys Phe Leu His Glu Arg Gln Pro Glu Leu Gln Ser Val Cys
35 40 45

Ile Ser Ala Ala Tyr Val Leu Ala Thr Pro Pro Glu Pro Ser Phe Ile
50 55 60

Leu Val Gly Phe Ser Glu Ala Gly Phe Ala Gln Val Ala Cys Phe Leu
65 70 75 80

Lys Tyr Leu Phe Cys Arg Pro Phe Thr Arg His Gly Tyr Phe Tyr Ser
85 90 95

Gly

<210> 395
<211> 187
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (167)
<223> Xaa equals any amino acid

<400> 395
Met Gly Phe Phe Leu Val Leu Val Met Glu Gln Ile Thr Leu Ala Tyr
1 5 10 15

Lys Glu Gln Ser Gly Pro Ser Pro Leu Glu Glu Thr Arg Ala Leu Leu
20 25 30

Gly Thr Val Asn Gly Gly Pro Gln His Trp His Asp Gly Pro Gly Val

35 40 45

Pro Gln Ala Ser Gly Ala Pro Ala Thr Pro Ser Ala Leu Arg Ala Cys
50 55 60

Val Leu Val Phe Ser Leu Ala Leu His Ser Val Phe Glu Gly Leu Ala
65 70 75 80

Val Gly Leu Gln Arg Asp Arg Ala Arg Ala Met Glu Leu Cys Leu Ala
85 90 95

Leu Leu Leu His Lys Gly Ile Leu Ala Val Ser Leu Ser Leu Arg Leu
100 105 110

Leu Gln Ser His Leu Arg Ala Gln Val Val Ala Gly Cys Gly Ile Leu
115 120 125

Phe Ser Cys Met Thr Pro Leu Gly Ile Gly Leu Gly Ala Ala Leu Ala
130 135 140

Glu Ser Ala Gly Pro Leu His Gln Leu Ala Gln Ser Val Leu Glu Gly
145 150 155 160

Met Ala Ala Gly Thr Phe Xaa Tyr Ile Thr Phe Leu Glu Ile Leu Leu
165 170 175

Phe His Pro Lys Phe Lys Gly Val Ser Arg Arg
180 185

<210> 396
<211> 46
<212> PRT
<213> Homo sapiens

<400> 396
Met Thr Leu Ser Leu Gln Leu Ala Glu Leu Val His Phe Val Cys Ala
1 5 10 15

Phe Gln Ser Gln Trp Thr Gly Val Tyr Pro Met Met Pro Pro Leu Lys
20 25 30

Pro Thr Glu Pro Leu Cys Phe Ala Cys Val Pro Cys Arg Val
35 40 45

<210> 397
<211> 152
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (66)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (77)

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<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (81)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (84)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (86)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (87)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (93)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (103)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (110)
<223> Xaa equals any amino acid

<400> 397
Met Asp His Ser Pro Thr Thr Gly Val Val Thr Val Ile Val Ile Leu
  1               5                  10                  15

Ile Ala Ile Ala Ala Leu Gly Ala Phe Asp Pro Gly Leu Leu Val Leu
             20                  25                  30

Pro Ala Ala Ala Ala His Gln Pro Val Arg Gly Arg Gly Glu His Arg
         35                  40                  45

Gly Gly Trp Gly Asp Gln Gly Thr Leu Pro Ala Gly Ala Val Phe Gly
     50                  55                  60

Gln Xaa Thr Val Arg Gly Glu Lys Gly Gln Ala Asp Xaa Ser Gln Thr
 65                  70                  75                  80

Xaa Arg Lys Xaa Thr Xaa Xaa Pro Gly Cys Lys Gly Xaa Leu Val Pro
                 85                  90                  95

Val Cys Lys Pro Ala Lys Xaa Gly Leu Gly Gly Ala Lys Xaa Ile Arg
            100                 105                 110

Met Arg Cys Cys Leu Arg Gly Arg Ala Asp Thr Cys Trp His Gly Leu
        115                 120                 125
```

Cys Gly Phe Arg Pro Ser His Ala Leu Met Pro Gly Asp Leu Ala Val
    130   135   140

Leu Gly Phe Pro Ser Ala Ser Arg
145   150

<210> 398
<211> 340
<212> PRT
<213> Homo sapiens

<400> 398
Met Ala Leu Arg Leu Leu Arg Arg Ala Ala Arg Gly Ala Ala Ala Ala
1   5   10   15

Ala Leu Leu Arg Leu Lys Ala Ser Leu Ala Ala Asp Ile Pro Arg Leu
            20   25   30

Gly Tyr Ser Ser Ser Ser His His Lys Tyr Ile Pro Arg Arg Ala Val
        35   40   45

Leu Tyr Val Pro Gly Asn Asp Glu Lys Lys Ile Lys Lys Ile Pro Ser
    50   55   60

Leu Asn Val Asp Cys Ala Val Leu Asp Cys Glu Asp Gly Val Ala Ala
65   70   75   80

Asn Lys Lys Asn Glu Ala Arg Leu Arg Ile Val Lys Thr Leu Glu Asp
                85   90   95

Ile Asp Leu Gly Pro Thr Glu Lys Cys Val Arg Val Asn Ser Val Ser
            100   105   110

Ser Gly Leu Ala Glu Glu Asp Leu Glu Thr Leu Leu Gln Ser Arg Val
        115   120   125

Leu Pro Ser Ser Leu Met Leu Pro Lys Val Glu Ser Pro Glu Glu Ile
    130   135   140

Gln Trp Phe Ala Asp Lys Phe Ser Phe His Leu Lys Gly Arg Lys Leu
145   150   155   160

Glu Gln Pro Met Asn Leu Ile Pro Phe Val Glu Thr Ala Met Gly Leu
                165   170   175

Leu Asn Phe Lys Ala Val Cys Glu Glu Thr Leu Lys Val Gly Pro Gln
            180   185   190

Val Gly Leu Phe Leu Asp Ala Val Val Phe Gly Gly Glu Asp Phe Arg
        195   200   205

Ala Ser Ile Gly Ala Thr Ser Ser Lys Glu Thr Leu Asp Ile Leu Tyr
    210   215   220

Ala Arg Gln Lys Ile Val Val Ile Ala Lys Ala Phe Gly Leu Gln Ala
225   230   235   240

Val Asp Leu Val Tyr Ile Asp Phe Arg Asp Gly Ala Gly Leu Leu Arg

245 250 255

Gln Ser Arg Glu Gly Ala Ala Met Gly Phe Thr Gly Lys Gln Val Ile
260 265 270

His Pro Asn Gln Ile Ala Val Val Gln Glu Gln Phe Ser Pro Ser Pro
275 280 285

Glu Lys Ile Lys Trp Ala Glu Glu Leu Ile Ala Ala Phe Lys Glu His
290 295 300

Gln Gln Leu Gly Lys Gly Ala Phe Thr Phe Gln Gly Ser Met Ile Asp
305 310 315 320

Met Pro Leu Leu Lys Gln Ala Gln Asn Thr Val Thr Leu Ala Thr Ser
325 330 335

Ile Lys Glu Lys
340

<210> 399
<211> 64
<212> PRT
<213> Homo sapiens

<400> 399
Met Val Arg His Ile Arg Glu Arg Arg Arg Gln Pro Leu Ala Phe Gln
1 5 10 15

Arg Val Leu Leu Ser Leu Cys Leu Leu Glu Gly Ile Trp His Ser Pro
20 25 30

Ala Ala Ala Ala Gly Gly Gly Ser His Cys Ser Ser Trp Pro Ser Leu
35 40 45

Tyr Thr Thr Phe Gln Arg Val Ser Leu Leu Glu Leu Asp Leu Gly Leu
50 55 60

<210> 400
<211> 44
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (16)
<223> Xaa equals any amino acid

<400> 400
Met Cys Leu Pro Leu Leu His Cys Thr Gly Ala Leu Trp Gly Lys Xaa
1 5 10 15

Val Leu Leu Phe Leu Tyr Cys Leu Ala Gln Ser Phe Ala Tyr Ser Arg
20 25 30

```
His Gln Thr Val Gly Leu Val Val His Asp Tyr Trp
        35                  40


<210> 401
<211> 221
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (184)
<223> Xaa equals any amino acid

<400> 401
Met Ala Gly Gly Val Arg Pro Leu Arg Gly Leu Arg Ala Leu Cys Arg
  1               5                  10                  15

Val Leu Leu Phe Leu Ser Gln Phe Cys Ile Leu Ser Gly Gly Glu Ser
            20                  25                  30

Thr Glu Ile Pro Pro Tyr Val Met Lys Cys Pro Ser Asn Gly Leu Cys
        35                  40                  45

Ser Arg Leu Pro Ala Asp Cys Ile Asp Cys Thr Thr Asn Phe Ser Cys
    50                  55                  60

Thr Tyr Gly Lys Pro Val Thr Phe Asp Cys Ala Val Lys Pro Ser Val
65                  70                  75                  80

Thr Cys Val Asp Gln Asp Phe Lys Ser Gln Lys Asn Phe Ile Ile Asn
                85                  90                  95

Met Thr Cys Arg Phe Cys Trp Gln Leu Pro Glu Thr Asp Tyr Glu Cys
            100                 105                 110

Thr Asn Ser Thr Ser Cys Met Thr Val Ser Cys Pro Arg Gln Arg Tyr
        115                 120                 125

Pro Ala Asn Cys Thr Val Arg Asp His Val His Cys Leu Gly Asn Arg
    130                 135                 140

Thr Phe Pro Lys Met Leu Tyr Cys Asn Trp Thr Gly Gly Tyr Lys Trp
145                 150                 155                 160

Ser Thr Ala Leu Ala Leu Ser Ile Thr Leu Gly Gly Phe Gly Ala Asp
                165                 170                 175

Arg Phe Tyr Leu Gly Gln Trp Xaa Glu Gly Leu Gly Lys Leu Phe Ser
            180                 185                 190

Phe Gly Gly Leu Gly Ile Trp Thr Leu Ile Asp Val Leu Leu Ile Gly
        195                 200                 205

Val Gly Tyr Val Gly Pro Ala Asp Gly Ser Leu Tyr Ile
    210                 215                 220
```

<210> 402
<211> 39
<212> PRT
<213> Homo sapiens

<400> 402
Met Trp Leu Thr Gln Pro Glu Ser Leu Ser Leu Cys Val Ser Val Ser
1 5 10 15

Gln Asp Trp Ala His Ile Leu Ala Leu Ser Ile Thr Met Leu Trp Asp
20 25 30

Phe Arg Glu Phe Pro His Leu
35

<210> 403
<211> 62
<212> PRT
<213> Homo sapiens

<400> 403
Met Glu Asn Val Cys Gln Ala Gly Phe Pro Ser Leu Leu His Leu Asn
1 5 10 15

Ile Thr Leu Thr Leu Leu Gly Leu Ala Gln Cys Tyr Leu Ala Asn Phe
20 25 30

Ser Ser Cys Arg Glu Gly Ser Glu His Tyr Leu Phe Phe Phe Phe Phe
35 40 45

Leu Leu Glu Pro Gly Leu His Lys Ala Met Ala Lys Phe Ser
50 55 60

<210> 404
<211> 64
<212> PRT
<213> Homo sapiens

<400> 404
Met Val Ser Pro Leu Ile Ser Ala Leu Phe His Val Pro Phe Leu Trp
1 5 10 15

Leu Gly Met Phe Phe Pro His Ser Leu Ser Gly Pro Phe Pro Ser His
20 25 30

Leu Arg Arg Ala Ser Ser Ser Arg Lys Pro Leu Val Lys Pro Pro Arg
35 40 45

Ala Arg Gln Tyr Pro Pro Leu Ala Ser Ser Gly Tyr Arg Gly Arg Ile
50 55 60

<210> 405

<211> 62
<212> PRT
<213> Homo sapiens

<400> 405
Met Lys Asn Ser Thr Ser Leu Leu Tyr Lys Leu Phe Ser Ser Leu Ser
1   5   10   15

Val Phe Ile Phe Lys Phe Leu Leu Leu Phe Tyr Thr Leu His Ile Ala
            20   25   30

Leu Gly Val Lys Ile Gln Tyr Lys Pro Leu Ala His Phe Ile Asp His
        35   40   45

Ser Cys Ile Gln Gln Val Ser Gln Val Gln Trp Ser Ile Pro
    50   55   60

<210> 406
<211> 139
<212> PRT
<213> Homo sapiens

<400> 406
Met Ala Leu Gly Ile Gln Lys Arg Phe Ser Pro Glu Val Leu Gly Leu
1   5   10   15

Cys Ala Ser Thr Ala Leu Val Trp Val Val Met Glu Val Leu Ala Leu
            20   25   30

Leu Leu Gly Leu Tyr Leu Ala Thr Val Arg Ser Asp Leu Ser Thr Phe
        35   40   45

His Leu Leu Ala Tyr Ser Gly Tyr Lys Tyr Val Gly Met Ile Leu Ser
    50   55   60

Val Leu Thr Gly Leu Leu Phe Gly Ser Asp Gly Tyr Tyr Val Ala Leu
65   70   75   80

Ala Trp Thr Ser Ser Ala Leu Met Tyr Phe Ile Val Arg Ser Leu Arg
                85   90   95

Thr Ala Ala Leu Gly Pro Asp Ser Met Gly Gly Pro Val Pro Arg Gln
            100   105   110

Arg Leu Gln Leu Tyr Leu Thr Leu Gly Ala Ala Ala Phe Gln Pro Leu
        115   120   125

Ile Ile Tyr Trp Leu Thr Phe His Leu Val Arg
    130   135

<210> 407
<211> 42
<212> PRT
<213> Homo sapiens

<400> 407
Met Arg Lys Glu Glu Gly Ile Ala His Leu Ser Ile Ala Phe Phe Val

1 5 10 15

Gln Val Leu Cys Leu Tyr Gln Leu Leu Pro Val Ile Leu Pro Gln Phe
20 25 30

Asn Leu Gly Ser Gly Lys Asn Met Asn Arg
35 40

<210> 408
<211> 121
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (30)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (32)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (87)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (101)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (115)
<223> Xaa equals any amino acid

<400> 408
Met Cys Ser His Ser Thr Leu Ile His Leu Tyr Leu Val Leu Pro Phe
1 5 10 15

Phe Phe Leu Phe Leu Pro Ser Ser Phe Pro Phe Pro Ser Xaa Ser Xaa
20 25 30

Ser Ser Ile Leu Pro Ser Leu Arg Leu Pro Pro Phe Phe Pro Pro Ser
35 40 45

Leu Phe Leu His Ser Ser Leu Pro Pro Ser Leu Ser His Pro Leu Gly
50 55 60

Leu Ser Ile Thr Ser Ser Arg Gln Ser Phe Leu Asp Tyr His His Leu
65 70 75 80

Cys Thr Lys His Leu Ser Xaa Thr Leu Cys Gly Leu Ile Tyr His Cys
85 90 95

Leu Asn Ile Phe Xaa Thr Arg Ala Val Met Trp His Met Gln Val Ser
100 105 110

Phe Leu Xaa Ile His Trp Leu Leu Pro
        115   120

<210> 409
<211> 71
<212> PRT
<213> Homo sapiens

<400> 409
Met Arg Ile His Phe Lys Ile Leu Val Leu Val Ile Tyr Phe Ile Leu
1   5   10   15

Leu Gly Ser Phe Ser Asp Arg Cys Ser Leu Leu Asp Cys Lys Ser Arg
            20   25   30

Ile Gln Arg Ile Phe Ile Cys Asn Ile Leu Asn Leu Ser Leu Val Ser
        35   40   45

Cys His Leu Cys Arg Tyr Ser Phe Asp Cys Leu Thr Arg Gly Lys Cys
    50   55   60

Phe Pro Leu Ser Phe Pro Ala
65   70

<210> 410
<211> 68
<212> PRT
<213> Homo sapiens

<400> 410
Met Leu Met Leu Leu Thr Leu Leu Val Leu Gly Met Val Trp Val Ala
1   5   10   15

Ser Ala Ile Val Asp Lys Asn Lys Ala Asn Arg Glu Ser Leu Tyr Asp
            20   25   30

Phe Trp Glu Tyr Tyr Leu Pro Tyr Leu Tyr Ser Cys Ile Ser Phe Leu
        35   40   45

Gly Val Leu Leu Leu Leu Ala Ala Gly Arg Pro Gly Gly Ala Ala Val
    50   55   60

Leu Leu Ser Leu
65

<210> 411
<211> 233
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (173)
<223> Xaa equals any amino acid

<400> 411
Met His Arg Gly Lys Leu Asp Cys Ala Gly Gly Ala Leu Leu Ser Ser
1 5 10 15

Tyr Leu Ile Val Leu Met Ile Leu Leu Ala Val Val Ile Cys Thr Val
20 25 30

Ser Ala Ile Met Cys Val Ser Met Arg Gly Thr Ile Cys Asn Pro Gly
35 40 45

Pro Arg Lys Ser Met Ser Lys Leu Leu Tyr Ile Arg Leu Ala Leu Phe
50 55 60

Phe Pro Glu Met Val Trp Ala Ser Leu Gly Ala Ala Trp Val Ala Asp
65 70 75 80

Gly Val Gln Cys Asp Arg Thr Val Val Asn Gly Ile Ile Ala Thr Val
85 90 95

Val Val Ser Trp Ile Ile Ile Ala Ala Thr Val Val Ser Ile Ile Ile
100 105 110

Val Phe Asp Pro Leu Gly Gly Lys Met Ala Pro Tyr Ser Ser Ala Gly
115 120 125

Pro Ser His Leu Asp Ser His Asp Ser Ser Gln Leu Leu Asn Gly Leu
130 135 140

Lys Thr Ala Ala Thr Ser Val Trp Glu Thr Arg Ile Lys Leu Leu Cys
145 150 155 160

Cys Cys Ile Gly Lys Asp Asp His Thr Arg Val Ala Xaa Ser Ser Thr
165 170 175

Ala Glu Leu Phe Ser Thr Tyr Phe Ser Asp Thr Asp Leu Val Pro Ser
180 185 190

Asp Ile Ala Ala Gly Leu Ala Leu Leu His Gln Gln Gln Asp Asn Ile
195 200 205

Arg Asn Asn Gln Asp Leu Pro Arg Trp Ser Ala Met Pro Gln Gly Ala
210 215 220

Pro Arg Lys Leu Ile Trp Met Gln Asn
225 230

<210> 412
<211> 66
<212> PRT
<213> Homo sapiens

<400> 412
Met Phe Val Glu Arg Trp Leu Pro Cys Phe Leu Val Val Ala Val Val
1 5 10 15

Val Trp Val Phe Ala Cys Gly Pro Val Glu Asp Lys Glu Asp Ser Phe
20 25 30

```
Gly Trp Ser Ser Tyr Phe Leu Ala Ser Gly Leu Pro Pro Leu Leu Phe
        35                  40                  45

Glu Ala Ser Gln Thr Arg Thr Val Arg Ala Gly Arg Leu Gly Val Phe
    50                  55                  60

Val Cys
65



&lt;210&gt; 413
&lt;211&gt; 90
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;220&gt;
&lt;221&gt; SITE
&lt;222&gt; (29)
&lt;223&gt; Xaa equals any amino acid

&lt;220&gt;
&lt;221&gt; SITE
&lt;222&gt; (30)
&lt;223&gt; Xaa equals any amino acid

&lt;220&gt;
&lt;221&gt; SITE
&lt;222&gt; (65)
&lt;223&gt; Xaa equals any amino acid

&lt;400&gt; 413
Met Leu Arg Cys Ser Phe Ser Ser Phe Leu Leu Cys His Thr Ile Leu
1               5                   10                  15

Leu Phe Leu Gly Ser Ser Ala His Leu Leu Val Glu Xaa Xaa Val Trp
            20                  25                  30

Gly Leu Tyr Glu Tyr Arg Ile Gly Asp Met Val Asp Gln Lys Ala Thr
        35                  40                  45

Phe Cys Val Gln Lys Gln Glu Cys Leu Phe Pro Leu Gly Ser Trp Val
    50                  55                  60

Xaa Arg Val Glu Gly Gly Ala Phe Ala Arg Glu Pro Pro Ser Ser Thr
65                  70                  75                  80

Gln Tyr Phe Pro Val Ser Cys Leu Tyr Gln
                85                  90



&lt;210&gt; 414
&lt;211&gt; 36
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 414
Met Gly Cys Thr Ala Leu Leu Leu Leu Phe His Leu Cys Val Pro Cys
1               5                   10                  15
```

Glu Pro Tyr Gly Thr His Glu Lys Glu Leu Val Pro Gly Leu Tyr Phe
20 25 30

Leu Val Tyr Arg
35

<210> 415
<211> 46
<212> PRT
<213> Homo sapiens

<400> 415
Met Cys Ile Pro Glu Ala Leu Gly Lys Asn Ser Leu Phe Leu Ser Ser
1 5 10 15

Thr Phe Leu Trp Leu Leu Ala Phe Phe Gly Leu Trp Ser His His Ser
20 25 30

Tyr Leu Glu Gly Gln His Leu Gln Ile Cys Phe Phe Phe Thr
35 40 45

<210> 416
<211> 82
<212> PRT
<213> Homo sapiens

<400> 416
Met Ala Ile Ser Cys Trp Ala Ser Leu Thr Val Lys Ser Leu Tyr Cys
1 5 10 15

Leu Leu Gly Phe Trp Trp Glu Ala Val Ile Ser Ser Asn Glu Leu Pro
20 25 30

Leu Pro Trp Ile Cys Gln Glu Ala Asp Gly Asn Leu Ala Asn Ser Gly
35 40 45

Arg Tyr Gln Ala Pro Ser Ser Ala Pro Val Thr Leu Phe Tyr Thr Cys
50 55 60

Gly Ser Thr Thr Val Cys Ser Glu Gly Gln Ser Leu Pro Leu Leu Cys
65 70 75 80

Phe Ser

<210> 417
<211> 57
<212> PRT
<213> Homo sapiens

<400> 417
Met Pro Pro His Arg Gln Thr Asp Gly Gln Met Gly Leu Pro Ala Pro
1 5 10 15

Ala Leu Trp Val Trp Gly Leu Leu Leu Ser Ser Ser Phe Gln Thr Leu

```
            20                  25                  30

Leu Pro Ala Phe Pro Lys Pro Pro Ala Leu Asn Leu Gly Cys Ser Thr
        35                  40                  45

Arg Pro Ile Pro Ser Phe Leu Lys Ile
    50                  55



<210> 418
<211> 81
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (44)
<223> Xaa equals any amino acid

<400> 418
Met Arg Met Arg Val Ala Val Ala Pro Arg Pro His Gln His Leu Val
  1               5                  10                  15

Val Ser Val Ser Trp Ile Leu Ala Ile Leu Ile Ser Val Ser Gly Tyr
            20                  25                  30

His Cys Phe His Leu Gln Phe Ser Tyr Met Val Xaa Asn Ile Phe Pro
        35                  40                  45

His Val Tyr Leu Ser Ser Ala Tyr Leu Leu Arg Pro Val Ile Cys Ser
    50                  55                  60

Asp Leu Leu Pro Val Phe Val Cys Leu His Val Cys Leu Cys Leu Ile
 65                  70                  75                  80

Phe



<210> 419
<211> 80
<212> PRT
<213> Homo sapiens

<400> 419
Met Cys Val Val Cys Val Cys Val Trp Cys Met Cys Val Cys Gly Val
  1               5                  10                  15

Cys Val Cys Leu Cys Val Cys Gly Val Cys Met Cys Ile Ser Leu Asn
            20                  25                  30

Glu Lys Leu Ala Pro Met Ile Met Glu Leu Thr Thr Pro Lys Val Cys
        35                  40                  45

Arg Gln Gln Ala Gly Gly Pro Gly Gly Pro Val Val Trp Leu Gln Pro
    50                  55                  60

Val Ser Glu Gly Leu Arg Thr Arg Arg Ala Gly Gly Ala Ala Ala Val
 65                  70                  75                  80
```

<210> 420
<211> 53
<212> PRT
<213> Homo sapiens

<400> 420
Met Ser Thr Phe Val Cys Val Cys Val Phe Cys Phe Val Leu Arg Ser
1   5   10   15

Glu Ala Arg Ala Lys Arg Lys Gln Asp Gln Arg Asn Thr Lys Arg Cys
            20   25   30

Leu Leu Thr Lys Gly Gln Arg Asp Leu Ser Val Asn Gln Ser Lys Ile
        35   40   45

Asn Arg Thr Ala Asn
    50

<210> 421
<211> 80
<212> PRT
<213> Homo sapiens

<400> 421
Met Ala Leu Trp Val Thr Cys Ile Leu Ser Leu Cys Thr Trp Phe Ser
1   5   10   15

Cys Leu Tyr Gly Ala Asp Ser Leu Ala Asn Lys Cys Leu Ser Ala Gly
            20   25   30

Ala Thr Arg Lys Ala Phe Pro Phe Cys Val Leu Phe Arg Asp Leu Glu
        35   40   45

Val Gly Leu Gly Phe Glu Gly Phe Val Thr His Leu Ala Cys Lys Leu
    50   55   60

Phe Cys Tyr Cys Glu Leu Ser Asp Ser Ala Leu Ser Leu Gly His Glu
65   70   75   80

<210> 422
<211> 320
<212> PRT
<213> Homo sapiens

<400> 422
Met Arg Gly Ser Val Glu Cys Thr Trp Gly Trp Gly His Cys Ala Pro
1   5   10   15

Ser Pro Leu Leu Leu Trp Thr Leu Leu Leu Phe Ala Ala Pro Phe Gly
20 25 30

Leu Leu Gly Glu Lys Thr Arg Gln Leu Leu Glu Phe Asp Ser Thr Asn
35 40 45

Val Ser Asp Thr Ala Ala Lys Pro Leu Gly Arg Pro Tyr Pro Pro Tyr
50 55 60

Ser Leu Ala Asp Phe Ser Trp Asn Asn Ile Thr Asp Ser Leu Asp Pro
65 70 75 80

Ala Thr Leu Ser Ala Thr Phe Gln Gly His Pro Met Asn Asp Pro Thr
85 90 95

Arg Thr Phe Ala Asn Gly Ser Leu Ala Phe Arg Val Gln Ala Phe Ser
100 105 110

Arg Ser Ser Arg Pro Ala Gln Pro Pro Arg Leu Leu His Thr Ala Asp
115 120 125

Thr Cys Gln Leu Glu Val Ala Leu Ile Gly Ala Ser Pro Arg Gly Asn
130 135 140

Arg Ser Leu Phe Gly Leu Glu Val Ala Thr Leu Gly Gln Gly Pro Asp
145 150 155 160

Cys Pro Ser Met Gln Glu Gln His Ser Ile Asp Asp Glu Tyr Ala Pro
165 170 175

Ala Val Phe Gln Leu Asp Gln Leu Leu Trp Gly Ser Leu Pro Ser Gly
180 185 190

Phe Ala Gln Trp Arg Pro Val Ala Tyr Ser Gln Lys Pro Gly Gly Arg
195 200 205

Glu Ser Ala Leu Pro Cys Gln Ala Ser Pro Leu His Pro Ala Leu Ala
210 215 220

Tyr Ser Leu Pro Gln Ser Pro Ile Val Arg Ala Phe Phe Gly Ser Gln
225 230 235 240

Asn Asn Phe Cys Ala Phe Asn Leu Thr Phe Gly Ala Ser Thr Gly Pro
245 250 255

Gly Tyr Trp Asp Gln His Tyr Leu Ser Trp Ser Met Leu Leu Gly Val
260 265 270

Gly Phe Pro Pro Val Asp Gly Leu Ser Pro Leu Val Leu Gly Ile Met
275 280 285

Ala Val Ala Leu Gly Ala Pro Gly Leu Met Leu Leu Gly Gly Gly Leu
290 295 300

Val Leu Leu Leu His His Lys Lys Tyr Ser Glu Tyr Gln Ser Ile Asn
305 310 315 320

<210> 423
<211> 115
<212> PRT
<213> Homo sapiens

<400> 423
Met Leu Ala Leu Ser Ser Ser Phe Leu Val Leu Ser Tyr Leu Leu Thr
1 5 10 15

Arg Trp Cys Gly Ser Val Gly Phe Ile Leu Ala Asn Cys Phe Asn Met
20 25 30

Gly Ile Arg Ile Thr Gln Ser Leu Cys Phe Ile His Arg Tyr Tyr Arg
35 40 45

Arg Ala Pro Thr Gly Pro Trp Leu Ala Cys Thr Tyr Arg Gln Ser Cys
50 55 60

Ser Gly His Leu Pro Ser Val Val Gly Leu Leu Leu Phe Arg Arg Tyr
65 70 75 80

Ser Ser Ala Val Ser Arg Ala Gly Gln Pro Asp Trp His Thr Leu Leu
85 90 95

Trp Gly Pro Ser Val Trp Glu Gln Leu Ser Gly Gln His Ser Ser Gln
100 105 110

Arg Pro Ser
115

<210> 424
<211> 402
<212> PRT
<213> Homo sapiens

<400> 424
Met Tyr Ser Gly Asn Arg Ser Gly Gly His Gly Tyr Trp Asp Gly Gly
1 5 10 15

Gly Ala Ala Gly Ala Glu Gly Pro Ala Pro Ala Gly Thr Leu Ser Pro
20 25 30

Ala Pro Leu Phe Ser Pro Gly Thr Tyr Glu Arg Leu Ala Leu Leu Leu
35 40 45

Gly Ser Ile Gly Leu Leu Gly Val Gly Asn Asn Leu Leu Val Leu Val
50 55 60

Leu Tyr Tyr Lys Phe Gln Arg Leu Arg Thr Pro Thr His Leu Leu Leu
65 70 75 80

Val Asn Ile Ser Leu Ser Asp Leu Leu Val Ser Leu Phe Gly Val Thr
85 90 95

Phe Thr Phe Val Ser Cys Leu Arg Asn Gly Trp Val Trp Asp Thr Val
100 105 110

Gly Cys Val Trp Asp Gly Phe Ser Gly Ser Leu Phe Gly Ile Val Ser

115 120 125

Ile Ala Thr Leu Thr Val Leu Ala Tyr Glu Arg Tyr Ile Arg Val Val
130 135 140

His Ala Arg Val Ile Asn Phe Ser Trp Ala Trp Arg Ala Ile Thr Tyr
145 150 155 160

Ile Trp Leu Tyr Ser Leu Ala Trp Ala Gly Ala Pro Leu Leu Gly Trp
165 170 175

Asn Arg Tyr Ile Leu Asp Val His Gly Leu Gly Cys Thr Val Asp Trp
180 185 190

Lys Ser Lys Asp Ala Asn Asp Ser Ser Phe Val Leu Phe Leu Phe Leu
195 200 205

Gly Cys Leu Val Val Pro Leu Gly Val Ile Ala His Cys Tyr Gly His
210 215 220

Ile Leu Tyr Ser Ile Arg Met Leu Arg Cys Val Glu Asp Leu Gln Thr
225 230 235 240

Ile Gln Val Ile Lys Ile Leu Lys Tyr Glu Lys Lys Leu Ala Lys Met
245 250 255

Cys Phe Leu Met Ile Phe Thr Phe Leu Val Cys Trp Met Pro Tyr Ile
260 265 270

Val Ile Cys Phe Leu Val Val Asn Gly His Gly His Leu Val Thr Pro
275 280 285

Thr Ile Ser Ile Val Ser Tyr Leu Phe Ala Lys Ser Asn Thr Val Tyr
290 295 300

Asn Pro Val Ile Tyr Val Phe Met Ile Arg Lys Phe Arg Arg Ser Leu
305 310 315 320

Leu Gln Leu Leu Cys Leu Arg Leu Leu Arg Cys Gln Arg Pro Ala Lys
325 330 335

Asp Leu Pro Ala Ala Gly Ser Glu Met Gln Ile Arg Pro Ile Val Met
340 345 350

Ser Gln Lys Asp Gly Asp Arg Pro Lys Lys Lys Val Thr Phe Asn Ser
355 360 365

Ser Ser Ile Ile Phe Ile Ile Thr Ser Asp Glu Ser Leu Ser Val Asp
370 375 380

Asp Ser Asp Lys Thr Asn Gly Ser Lys Val Asp Val Ile Gln Val Arg
385 390 395 400

Pro Leu

<210> 425
<211> 76
<212> PRT

<213> Homo sapiens

<400> 425
Met Gly Ala His Ser Phe Gly Phe Gln Leu Phe Met Ser Val Ser Val
1   5   10   15

Leu Trp Gly Arg Leu Cys Leu Tyr Gly Arg Phe Ser Val Ile Thr Phe
            20   25   30

Ala Ser Pro Pro Thr Thr Phe Met Asp Ile Gln Cys Cys Phe Ala Leu
        35   40   45

Gln Leu Glu Arg Arg Asp Gly Gln Leu Val Thr Leu Ser His Ile Ala
    50   55   60

Thr Phe Ile Cys Ser Gly Lys Lys Leu Asp Arg Trp
65   70   75

<210> 426
<211> 41
<212> PRT
<213> Homo sapiens

<400> 426
Met Ala Val Pro Leu Phe Leu Tyr Ile Phe Thr Leu Leu Pro Leu Leu
1   5   10   15

Pro Phe Leu Leu Ser Leu Cys Phe Ser Pro Leu Thr Val Lys Arg Ser
            20   25   30

Ser Ser Ser Glu Ser Lys Ser Ser Leu
        35   40

<210> 427
<211> 35
<212> PRT
<213> Homo sapiens

<400> 427
Ile Tyr Ser Ser Gly Tyr Phe Gln Ile Tyr Asn Met Leu Leu Leu Thr
1   5   10   15

Ile Leu Ile Leu Leu Cys Asn Arg Thr Pro Glu Leu Ile Pro Gly Phe
            20   25   30

Tyr Ile Arg
        35

<210> 428
<211> 484
<212> PRT
<213> Homo sapiens

<400> 428
Met Pro Arg His Leu Ser Gly Leu Leu Leu Leu Leu Trp Pro Leu Leu

```
 1               5                   10                  15

Leu Leu Leu Pro Pro Thr Pro Ala Ala Pro Gly Pro Leu Ala Arg Pro
            20                  25                  30

Gly Leu Arg Arg Leu Gly Thr Arg Gly Pro Gly Gly Ser Pro Gly Arg
        35                  40                  45

Arg Pro Val Ser Ala Val Pro Thr Arg Ala Pro Tyr Ser Gly Ala Gly
    50                  55                  60

Gln Pro Gly Gly Ala Arg Gly Ala Gly Val Cys Arg Ser Arg Pro Leu
65                  70                  75                  80

Asp Leu Val Phe Ile Ile Asp Ser Ser Arg Ser Val Arg Pro Leu Glu
                85                  90                  95

Phe Thr Lys Val Lys Thr Phe Val Ser Gln Ile Ile Asp Thr Leu Asp
            100                 105                 110

Ile Gly Ala Ala Asp Thr Arg Val Ala Val Val Asn Tyr Ala Ser Thr
        115                 120                 125

Val Lys Ile Glu Phe His Leu Gln Thr His Ser Asp Lys Gln Ser Leu
    130                 135                 140

Lys Gln Ala Val Ala Arg Ile Thr Pro Leu Ser Thr Gly Thr Met Ser
145                 150                 155                 160

Gly Leu Ala Ile Gln Thr Ala Met Asp Glu Ala Phe Thr Val Glu Ala
                165                 170                 175

Gly Ala Arg Gly Pro Thr Ser Asn Ile Pro Lys Val Ala Ile Ile Val
            180                 185                 190

Thr Asp Gly Arg Pro Gln Asp Gln Val Asn Glu Val Ala Ala Arg Ala
        195                 200                 205

Arg Ala Ser Gly Ile Glu Leu Tyr Ala Val Gly Val Asp Arg Ala Asp
    210                 215                 220

Met Glu Ser Leu Lys Met Met Ala Ser Glu Pro Leu Asp Glu His Val
225                 230                 235                 240

Phe Tyr Val Glu Thr Tyr Gly Val Ile Glu Lys Leu Ser Ser Arg Phe
                245                 250                 255

Gln Glu Thr Phe Cys Ala Leu Asp Pro Cys Val Leu Gly Thr His Arg
            260                 265                 270

Cys Gln His Val Cys Val Ser Asp Gly Glu Gly Lys His His Cys Glu
        275                 280                 285

Cys Ser Gln Gly Tyr Ser Leu Asn Ala Asp Gln Lys Thr Cys Ser Ala
    290                 295                 300

Ile Asp Lys Cys Ala Leu Asn Thr His Gly Cys Glu His Ile Cys Val
305                 310                 315                 320

Asn Asp Arg Thr Gly Ser Tyr His Cys Glu Cys Tyr Glu Gly Tyr Thr
                325                 330                 335
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Leu Asn Gln Asp Arg Lys Thr Cys Ser Ala Gln Asp Gln Cys Ala Phe
340 345 350

Gly Thr His Gly Cys Gln His Ile Cys Val Asn Asp Arg Asp Gly Ser
355 360 365

His His Cys Glu Cys Tyr Glu Gly Tyr Thr Leu Asn Ala Asp Asn Lys
370 375 380

Thr Cys Ser Val Arg Ser Glu Cys Ala Gly Gly Ser His Gly Cys Gln
385 390 395 400

His Leu Cys Val Asp Asp Gly Pro Ala Ala Tyr His Cys Asp Cys Phe
405 410 415

Pro Gly Tyr Thr Leu Thr Glu Asp Arg Arg Thr Cys Ala Ala Ile Glu
420 425 430

Glu Ala Arg Arg Leu Val Ser Thr Glu Asp Ala Cys Gly Cys Glu Ala
435 440 445

Thr Leu Ala Phe Gln Glu Arg Ala Ser Ser Tyr Leu Gln Arg Leu Asn
450 455 460

Ala Lys Leu Asp Asp Ile Leu Gly Lys Leu Gln Ala Asp Ala Tyr Gly
465 470 475 480

Gln Ile His Arg

<210> 429
<211> 129
<212> PRT
<213> Homo sapiens

<400> 429
Met Ala Pro Ser Gly Pro Leu Leu Leu Val Leu Leu Val Pro Leu Ala
1 5 10 15

Ala Ala Arg Ala Gly Pro Tyr Phe Arg Pro Gly Arg Gly Cys Arg Leu
20 25 30

Pro Leu Arg Gly Asp Gln Leu Ser Gly Leu Gly Arg Arg Thr Tyr Pro
35 40 45

Arg Pro His Glu Tyr Leu Ser Pro Ser Asp Leu Pro Lys Ser Trp Asp
50 55 60

Trp Arg Asn Val Asn Gly Val Asn Tyr Ala Ser Ala Thr Arg Asn Gln
65 70 75 80

His Ile Pro Gln Tyr Cys Gly Ser Cys Trp Ala His Gly Ser Thr Ser
85 90 95

Ala Met Ala Gly Pro Asp Gln His Gln Glu Lys Gly Gly Val Ala Leu
100 105 110

His Pro Ala Val Arg Ala Ala Arg Pro Arg Leu Arg Gln Arg Gly Leu

115 120 125

Leu

<210> 430
<211> 164
<212> PRT
<213> Homo sapiens

<400> 430
Met Thr Thr Trp Ser Cys Leu Val Ala Met Ile Val Ser Gly Val Ile
1 5 10 15

Thr Ala Val Trp Ala Val Arg Ala Ala Pro Ile Trp Arg Ser Gln Val
20 25 30

Lys Gln Lys Met Arg Ile Gly Lys Gln Gly Asn Cys Arg Pro Pro Arg
35 40 45

Cys Ile Cys Ser Ala Leu Gly Leu Leu Ala Pro Trp Met Ala Val Val
50 55 60

Leu Ser Gln Leu Ser Val Arg Cys Val Val Ser Trp Val Gln Gly Lys
65 70 75 80

Pro Ser Ser Pro Arg Pro Arg Gly Ser Ala Ala Ser Pro Ala Pro Gly
85 90 95

Ala Thr Pro Pro Thr Pro Arg Lys Pro Val Ser Trp Leu Gly Tyr Arg
100 105 110

Glu Asn His Arg Pro Lys Lys Pro Lys Ser Cys Thr Arg Leu Pro Gly
115 120 125

Leu Pro Lys Leu Glu Pro Ser Ser Thr Leu Lys Gly Gln Asp Ser Trp
130 135 140

Gln Met Gly His Gln Gln Asp Lys Thr Leu Trp Ser Trp Ala Ser Thr
145 150 155 160

Gly Gly Ser Ser

<210> 431
<211> 56
<212> PRT
<213> Homo sapiens

<400> 431
Met Pro Leu Glu Glu Ser Phe Glu Ile Val Leu Lys Leu Val Pro Leu
1 5 10 15

Leu Gly Leu Glu Leu Phe Phe Phe Leu Phe Ile Ile Asn Gly Tyr Ile
20 25 30

Asn Val Tyr Cys Pro Ser Gln Tyr Phe Ile Tyr Ala Lys Asp Ser Leu

35 40 45

Ala Gly Leu Ala Leu Ile Pro Gln
50 55

<210> 432
<211> 40
<212> PRT
<213> Homo sapiens

<400> 432
Met Val Ala Met Val Phe Leu Lys Ile Ser Val Leu Pro Leu Met Cys
1 5 10 15

Arg Gly Gln Thr Lys His Lys Val Leu Arg Asp His Ala Tyr Pro Arg
20 25 30

Val Ser Gln Lys Arg Gly His Ile
35 40

<210> 433
<211> 41
<212> PRT
<213> Homo sapiens

<400> 433
Met Cys Val Cys Leu Ile Cys Ser Ile Cys Gln Phe Leu Trp Cys Lys
1 5 10 15

Tyr Ser His Tyr Ser Cys Phe Gln Ala Asn Ile Val Ile Pro Gln Lys
20 25 30

Met Glu Leu Gly Arg His Asn Gln Asp
35 40

<210> 434
<211> 211
<212> PRT
<213> Homo sapiens

<400> 434
Met Val Phe Leu Lys Phe Phe Cys Met Ser Phe Phe Cys His Leu Cys
1 5 10 15

Gln Gly Tyr Phe Asp Gly Pro Leu Tyr Pro Glu Met Ser Asn Gly Thr
20 25 30

Leu His His Tyr Phe Val Pro Asp Gly Asp Tyr Glu Glu Asn Asp Asp
35 40 45

Pro Glu Lys Cys Gln Leu Leu Phe Arg Val Ser Asp His Arg Arg Cys
50 55 60

Ser Gln Gly Glu Gly Ser Gln Val Gly Ser Leu Leu Ser Leu Thr Leu
65 70 75 80

Arg Glu Glu Phe Thr Val Leu Gly His Gln Val Glu Asp Ala Gly Arg
85 90 95

Val Leu Glu Gly Ile Ser Lys Ser Ile Ser Tyr Asp Leu Asp Gly Glu
100 105 110

Glu Ser Tyr Gly Lys Tyr Leu Arg Arg Glu Ser His Gln Ile Gly Asp
115 120 125

Ala Tyr Ser Asn Ser Asp Lys Ser Leu Thr Glu Leu Glu Ser Lys Phe
130 135 140

Lys Gln Gly Gln Glu Gln Asp Ser Arg Gln Glu Ser Arg Leu Asn Glu
145 150 155 160

Asp Phe Leu Gly Met Leu Val His Thr Arg Ser Leu Leu Lys Glu Thr
165 170 175

Leu Asp Ile Ser Val Gly Leu Arg Asp Lys Tyr Glu Leu Leu Ala Leu
180 185 190

Thr Ile Arg Ser His Gly Thr Arg Leu Gly Arg Leu Lys Asn Asp Tyr
195 200 205

Leu Lys Val
210

<210> 435
<211> 53
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (49)
<223> Xaa equals any amino acid

<400> 435
Met Ser His His Ala Gly Leu Gly Gly Gly Ile Leu Phe Ser Leu Lys
1 5 10 15

Ile Ser Phe Phe Ile Ala Leu Ala Val Val Gly Gly Ser Arg Gly Val
20 25 30

Asn Asp Cys Gln Leu Gly Gly Cys Arg Val Gly Ser Cys Pro Arg Val
35 40 45

Xaa Val Arg Val Ala
50

<210> 436
<211> 48
<212> PRT
<213> Homo sapiens

<400> 436

Met Met Leu Tyr Gln Asn Met Leu Leu Tyr Phe Arg Ile Ile Gly Val
1 5 10 15

Leu Ala Leu Asn Phe Ser Ile Ser Pro Ile Phe Phe His Gly Ser Leu
20 25 30

Gly Lys Leu Tyr Val Tyr Ser Ala Ala Lys Tyr Ser Leu Glu Leu Lys
35 40 45

<210> 437
<211> 201
<212> PRT
<213> Homo sapiens

<400> 437
Met Lys Leu Leu Ile Leu Phe Leu Ser His Leu Leu Ser Leu Ala Phe
1 5 10 15

Gly Ile Leu Cys Leu Ser Val Thr Val Ile Leu Ser Leu Leu Leu Ser
20 25 30

Phe Ser Lys Arg Gly Phe Ser Val Arg Ser Phe Gly Thr Gly Thr His
35 40 45

Val Lys Leu Pro Gly Pro Ala Pro Asp Lys Pro Asn Val Tyr Asp Phe
50 55 60

Lys Thr Thr Tyr Asp Gln Met Tyr Asn Asp Leu Leu Arg Lys Asp Lys
65 70 75 80

Glu Leu Tyr Thr Gln Asn Gly Ile Leu His Met Leu Asp Arg Asn Lys
85 90 95

Arg Ile Lys Pro Arg Pro Glu Arg Phe Gln Asn Cys Lys Asp Leu Phe
100 105 110

Asp Leu Ile Leu Thr Cys Glu Glu Arg Val Tyr Asp Gln Val Val Glu
115 120 125

Asp Leu Asn Ser Arg Glu Gln Glu Thr Cys Gln Pro Val His Val Val
130 135 140

Asn Val Asp Ile Gln Asp Asn His Glu Glu Ala Thr Leu Gly Ala Phe
145 150 155 160

Leu Ile Cys Glu Leu Cys Gln Cys Ile Gln His Thr Glu Asp Met Glu
165 170 175

Asn Glu Ile Asp Glu Leu Leu Gln Glu Phe Glu Glu Lys Ser Gly Arg
180 185 190

Thr Phe Leu His Thr Val Cys Phe Tyr
195 200

<210> 438
<211> 420
<212> PRT
<213> Homo sapiens

<400> 438
Met Ala Pro Trp Pro Pro Lys Gly Leu Val Pro Ala Val Leu Trp Gly
1 5 10 15

Leu Ser Leu Phe Leu Asn Leu Pro Gly Pro Ile Trp Leu Gln Pro Ser
20 25 30

Pro Pro Pro Gln Ser Ser Pro Pro Pro Gln Pro His Pro Cys His Thr
35 40 45

Cys Arg Gly Leu Val Asp Ser Phe Asn Lys Gly Leu Glu Arg Thr Ile
50 55 60

Arg Asp Asn Phe Gly Gly Gly Asn Thr Ala Trp Glu Glu Glu Asn Leu
65 70 75 80

Ser Lys Tyr Lys Asp Ser Glu Thr Arg Leu Val Glu Val Leu Glu Gly
85 90 95

Val Cys Ser Lys Ser Asp Phe Glu Cys His Arg Leu Leu Glu Leu Ser
100 105 110

Glu Glu Leu Val Glu Ser Trp Trp Phe His Lys Gln Gln Glu Ala Pro
115 120 125

Asp Leu Phe Gln Trp Leu Cys Ser Asp Ser Leu Lys Leu Cys Cys Pro
130 135 140

Ala Gly Thr Phe Gly Pro Ser Cys Leu Pro Cys Pro Gly Gly Thr Glu
145 150 155 160

Arg Pro Cys Gly Gly Tyr Gly Gln Cys Glu Gly Glu Gly Thr Arg Gly
165 170 175

Gly Ser Gly His Cys Asp Cys Gln Ala Gly Tyr Gly Gly Glu Ala Cys
180 185 190

Gly Gln Cys Gly Leu Gly Tyr Phe Glu Ala Glu Arg Asn Ala Ser His
195 200 205

Leu Val Cys Ser Ala Cys Phe Gly Pro Cys Ala Arg Cys Ser Gly Pro
210 215 220

Glu Glu Ser Asn Cys Leu Gln Cys Lys Lys Gly Trp Ala Leu His His
225 230 235 240

Leu Lys Cys Val Asp Ile Asp Glu Cys Gly Thr Glu Gly Ala Asn Cys
245 250 255

Gly Ala Asp Gln Phe Cys Val Asn Thr Glu Gly Ser Tyr Glu Cys Arg
260 265 270

Asp Cys Ala Lys Ala Cys Leu Gly Cys Met Gly Ala Gly Pro Gly Arg
275 280 285

Cys Lys Lys Cys Ser Pro Gly Tyr Gln Gln Val Gly Ser Lys Cys Leu

290 295 300

Asp Val Asp Glu Cys Glu Thr Glu Val Cys Pro Gly Glu Asn Lys Gln
305 310 315 320

Cys Glu Asn Thr Glu Gly Gly Tyr Arg Cys Ile Cys Ala Glu Gly Tyr
325 330 335

Lys Gln Met Glu Gly Ile Cys Val Lys Glu Gln Ile Pro Glu Ser Ala
340 345 350

Gly Phe Phe Ser Glu Met Thr Glu Asp Glu Leu Val Val Leu Gln Gln
355 360 365

Met Phe Phe Gly Ile Ile Ile Cys Ala Leu Ala Thr Leu Ala Ala Lys
370 375 380

Gly Asp Leu Val Phe Thr Ala Ile Phe Ile Gly Ala Val Ala Ala Met
385 390 395 400

Thr Gly Tyr Trp Leu Ser Glu Arg Ser Asp Arg Val Leu Glu Gly Phe
405 410 415

Ile Lys Gly Arg
420

<210> 439
<211> 102
<212> PRT
<213> Homo sapiens

<400> 439
Met Thr Val Arg Arg Leu Ser Leu Leu Cys Arg Asp Leu Trp Ala Leu
1 5 10 15

Trp Leu Leu Leu Lys Ala Gly Ala Val Arg Gly Ala Arg Ala Gly Pro
20 25 30

Arg Leu Pro Gly Arg Cys Cys Gly Ala Thr Cys Gly Asp Ala Gly Arg
35 40 45

Gly Trp Thr Phe Trp Ala Gln Pro Cys Pro Gln Arg Leu Leu Gly Gln
50 55 60

Lys Pro Gly Ala Gly Gly Cys Arg Gly Trp Val Leu Gly Trp Val Pro
65 70 75 80

Pro Arg Pro Glu Glu Pro Cys Ser Leu Ala Gly Lys Val Cys Thr Gly
85 90 95

Leu Ala Arg Trp Met Val
100

<210> 440
<211> 53
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (11)
<223> Xaa equals any amino acid

<400> 440
Met Cys Lys Ala Val Cys Lys His Arg Leu Xaa Leu Phe Ala Val Ser
1 5 10 15

Ser Phe Ser Leu Gly Leu Gly Trp Val Cys Val Leu Val Leu Met Leu
20 25 30

Trp Pro Val Arg Leu Ser Leu Ala Pro Arg Pro Val Gln Leu Gln Gln
35 40 45

Arg Arg Ser His Cys
50

<210> 441
<211> 472
<212> PRT
<213> Homo sapiens

<400> 441
Met Lys Phe Leu Ile Phe Ala Phe Phe Gly Gly Val His Leu Leu Ser
1 5 10 15

Leu Cys Ser Gly Lys Ala Ile Cys Lys Asn Gly Ile Ser Lys Arg Thr
20 25 30

Phe Glu Glu Ile Lys Glu Glu Ile Ala Ser Cys Gly Asp Val Ala Lys
35 40 45

Ala Ile Ile Asn Leu Ala Val Tyr Gly Lys Ala Gln Asn Arg Ser Tyr
50 55 60

Glu Arg Leu Ala Leu Leu Val Asp Thr Val Gly Pro Arg Leu Ser Gly
65 70 75 80

Ser Lys Asn Leu Glu Lys Ala Ile Gln Ile Met Tyr Gln Asn Leu Gln
85 90 95

Gln Asp Gly Leu Glu Lys Val His Leu Glu Pro Val Arg Ile Pro His
100 105 110

Trp Glu Arg Gly Glu Glu Ser Ala Val Met Leu Glu Pro Arg Ile His
115 120 125

Lys Ile Ala Ile Leu Gly Leu Gly Ser Ser Ile Gly Thr Pro Pro Glu
130 135 140

Gly Ile Thr Ala Glu Val Leu Val Val Thr Ser Phe Asp Glu Leu Gln
145 150 155 160

Arg Arg Ala Ser Glu Ala Arg Gly Lys Ile Val Val Tyr Asn Gln Pro
165 170 175

Tyr Ile Asn Tyr Ser Arg Thr Val Gln Tyr Arg Thr Gln Gly Ala Val

180 185 190

Glu Ala Ala Lys Val Gly Ala Leu Ala Ser Leu Ile Arg Ser Val Ala
195 200 205

Ser Phe Ser Ile Tyr Ser Pro His Thr Gly Ile Gln Glu Tyr Gln Asp
210 215 220

Gly Val Pro Lys Ile Pro Thr Ala Cys Ile Thr Val Glu Asp Ala Glu
225 230 235 240

Met Met Ser Arg Met Ala Ser His Gly Ile Lys Ile Val Ile Gln Leu
245 250 255

Lys Met Gly Ala Lys Thr Tyr Pro Asp Thr Asp Ser Phe Asn Thr Val
260 265 270

Ala Glu Ile Thr Gly Ser Lys Tyr Pro Glu Gln Val Val Leu Val Ser
275 280 285

Gly His Leu Asp Ser Trp Asp Val Gly Gln Gly Ala Met Asp Asp Gly
290 295 300

Gly Gly Ala Phe Ile Ser Trp Glu Ala Leu Ser Leu Ile Lys Asp Leu
305 310 315 320

Gly Leu Arg Pro Lys Arg Thr Leu Arg Leu Val Leu Trp Thr Ala Glu
325 330 335

Glu Gln Gly Gly Val Gly Ala Phe Gln Tyr Tyr Gln Leu His Lys Val
340 345 350

Asn Ile Ser Asn Tyr Ser Leu Val Met Glu Ser Asp Ala Gly Thr Phe
355 360 365

Leu Pro Thr Gly Leu Gln Phe Thr Gly Ser Glu Lys Ala Arg Ala Ile
370 375 380

Met Glu Glu Val Met Ser Leu Leu Gln Pro Leu Asn Ile Thr Gln Val
385 390 395 400

Leu Ser His Gly Glu Gly Thr Asp Ile Asn Phe Trp Ile Gln Ala Gly
405 410 415

Val Pro Gly Ala Ser Leu Leu Asp Asp Leu Tyr Lys Tyr Phe Phe Phe
420 425 430

His His Ser His Gly Asp Thr Met Thr Val Met Asp Pro Lys Gln Met
435 440 445

Asn Val Ala Ala Ala Val Trp Ala Val Val Ser Tyr Val Val Ala Asp
450 455 460

Met Glu Glu Met Leu Pro Arg Ser
465 470

<210> 442
<211> 359
<212> PRT

<213> Homo sapiens

<400> 442

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Met Lys Leu Gly Cys Val Leu Met Ala Trp Ala Leu Tyr Leu Ser Leu
1               5                   10                  15

Gly Val Leu Trp Val Ala Gln Met Leu Leu Ala Ala Ser Phe Glu Thr
            20                  25                  30

Leu Gln Cys Glu Gly Pro Val Cys Thr Glu Glu Ser Ser Cys His Thr
        35                  40                  45

Glu Asp Asp Leu Thr Asp Ala Arg Glu Ala Gly Phe Gln Val Lys Ala
    50                  55                  60

Tyr Thr Phe Ser Glu Pro Phe His Leu Ile Val Ser Tyr Asp Trp Leu
65                  70                  75                  80

Ile Leu Gln Gly Pro Ala Lys Pro Val Phe Glu Gly Asp Leu Leu Val
                85                  90                  95

Leu Arg Cys Gln Ala Trp Gln Asp Trp Pro Leu Thr Gln Val Thr Phe
            100                 105                 110

Tyr Arg Asp Gly Ser Ala Leu Gly Pro Pro Gly Pro Asn Arg Glu Phe
        115                 120                 125

Ser Ile Thr Val Val Gln Lys Ala Asp Ser Gly His Tyr His Cys Ser
    130                 135                 140

Gly Ile Phe Gln Ser Pro Gly Pro Gly Ile Pro Glu Thr Ala Ser Val
145                 150                 155                 160

Val Ala Ile Thr Val Gln Glu Leu Phe Pro Ala Pro Ile Leu Arg Ala
                165                 170                 175

Val Pro Ser Ala Glu Pro Gln Ala Gly Gly Pro Met Thr Leu Ser Cys
            180                 185                 190

Gln Thr Lys Leu Pro Leu Gln Arg Ser Ala Ala Arg Leu Leu Phe Ser
        195                 200                 205

Phe Tyr Lys Asp Gly Arg Ile Val Gln Ser Arg Gly Leu Ser Ser Glu
    210                 215                 220

Phe Gln Ile Pro Thr Ala Ser Glu Asp His Ser Gly Ser Tyr Trp Cys
225                 230                 235                 240

Glu Ala Ala Thr Glu Asp Asn Gln Val Trp Lys Gln Ser Pro Gln Leu
                245                 250                 255

Glu Ile Arg Val Gln Gly Ala Ser Ser Ser Ala Ala Pro Pro Thr Leu
            260                 265                 270

Asn Pro Ala Pro Gln Lys Ser Ala Ala Pro Gly Thr Ala Pro Glu Glu
        275                 280                 285

Ala Pro Gly Pro Leu Pro Pro Pro Pro Thr Pro Ser Ser Glu Asp Pro
    290                 295                 300

Gly Phe Ser Ser Pro Leu Gly Met Pro Asp Pro His Leu Tyr His Gln
```

305 310 315 320

Met Gly Leu Leu Leu Lys His Met Gln Asp Val Arg Val Leu Leu Gly
325 330 335

His Leu Leu Met Glu Leu Arg Glu Leu Ser Gly His Arg Lys Pro Gly
340 345 350

Thr Thr Lys Ala Thr Ala Glu
355

<210> 443
<211> 379
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (283)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (303)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (307)
<223> Xaa equals any amino acid

<400> 443
Met Gly Tyr Ile Asp Asp Pro Asp Lys Tyr His Gln Gly Phe Glu Leu
1 5 10 15

Leu Leu Ser Ala Leu Gly Asp Pro Ser Glu Arg Val Val Ser Ala Thr
20 25 30

His Gln Val Phe Leu Pro Ala Tyr Ala Ala Trp Thr Thr Glu Leu Gly
35 40 45

Asn Leu Gln Ser His Leu Ile Leu Thr Leu Leu Asn Lys Ile Glu Lys
50 55 60

Leu Leu Arg Glu Gly Glu His Gly Leu Asp Glu His Lys Leu His Met
65 70 75 80

Tyr Leu Ser Ala Leu Gln Ser Leu Ile Pro Ser Leu Phe Ala Leu Val
85 90 95

Leu Gln Asn Ala Pro Phe Ser Ser Lys Ala Lys Leu His Gly Glu Val
100 105 110

Pro Gln Ile Glu Val Thr Arg Phe Pro Arg Pro Met Ser Pro Leu Gln
115 120 125

Asp Val Ser Thr Ile Ile Gly Ser Arg Glu Gln Leu Ala Val Leu Leu
130 135 140

Gln Leu Tyr Asp Tyr Gln Leu Glu Gln Glu Gly Thr Thr Gly Trp Glu
145 150 155 160

Ser Leu Leu Trp Val Val Asn Gln Leu Leu Pro Gln Leu Ile Glu Ile
165 170 175

Val Gly Lys Ile Asn Val Thr Ser Thr Ala Cys Val His Glu Phe Ser
180 185 190

Arg Phe Phe Trp Arg Leu Cys Arg Thr Phe Gly Lys Ile Phe Thr Asn
195 200 205

Thr Lys Val Lys Pro Gln Phe Gln Glu Ile Leu Arg Leu Ser Glu Glu
210 215 220

Asn Ile Asp Ser Ser Ala Gly Asn Gly Val Leu Thr Lys Ala Thr Val
225 230 235 240

Pro Ile Tyr Ala Thr Gly Val Leu Thr Cys Tyr Ile Gln Glu Glu Asp
245 250 255

Arg Lys Leu Leu Val Gly Phe Leu Glu Asp Val Met Thr Leu Leu Ser
260 265 270

Leu Ser His Ala Pro Leu Asp Ser Leu Lys Xaa Ser Phe Val Glu Leu
275 280 285

Gly Ala Asn Gln Ala Tyr His Glu Leu Leu Leu Thr Val Leu Xaa Tyr
290 295 300

Gly Val Xaa His Thr Ser Ala Leu Val Arg Cys Thr Ala Ala Arg Met
305 310 315 320

Phe Glu Leu Leu Val Lys Gly Val Asn Glu Thr Leu Val Ala Gln Arg
325 330 335

Val Val Pro Ala Leu Ile Thr Leu Ser Ser Asp Pro Glu Ile Ser Val
340 345 350

Arg Ile Ala Thr Ile Pro Ala Phe Gly Thr Ile Met Glu Thr Val Ile
355 360 365

Gln Arg Glu Leu Leu Glu Arg Val Lys Met Gln
370 375

<210> 444
<211> 48
<212> PRT
<213> Homo sapiens

<400> 444
Met Ser Thr Val Thr Trp Leu Leu Lys Leu Phe Thr Gln Phe Met Phe
1 5 10 15

Pro Pro Thr Val Ser Asn Ser His Thr Cys Ala Arg Tyr Tyr Val Phe
20 25 30

Asn Phe Cys Leu Ile Ile Ser Phe Asn Phe Asn Phe His Tyr His Trp
35 40 45

<210> 445
<211> 142
<212> PRT
<213> Homo sapiens

<400> 445
Met Gly Cys Leu Val Trp Gly Pro Ser Trp Pro Pro Leu Ser Leu Leu
1 5 10 15

Ala Ser Leu Leu His Ser Gly Ile Ala Gly Arg Cys Leu Leu Cys Leu
20 25 30

Phe Lys Gly Leu Ala Ala Ala Ala Ser Leu Gln Ile Arg Asp Leu Ala
35 40 45

Ser Arg Leu Thr Thr Gly Pro Arg Thr Cys Arg Val Gln Pro Pro Pro
50 55 60

His Pro Gln Ser Ser Pro Pro Trp Pro Gly Pro Pro Gly Ala Glu Thr
65 70 75 80

Cys Arg Pro Leu Ser Arg Thr Val Gly Gly Val Cys Pro Ser Asp Trp
85 90 95

Pro Val Ser Trp Leu Leu Leu Pro Pro Leu Pro Glu Val Val Thr Cys
100 105 110

Ser Cys Pro Arg Ile Lys Ala Arg Pro Glu Arg Thr Pro Glu Leu Leu
115 120 125

Cys Ala Trp Gly Gly Arg Gly Lys His Ser Gln Leu Val Ala
130 135 140

<210> 446
<211> 399
<212> PRT
<213> Homo sapiens

<400> 446
Met Gly Ile Leu Leu Gly Leu Leu Leu Leu Gly His Leu Thr Val Asp
1 5 10 15

Thr Tyr Gly Arg Pro Ile Leu Glu Val Pro Glu Ser Val Thr Gly Pro
20 25 30

Trp Lys Gly Asp Val Asn Leu Pro Cys Thr Tyr Asp Pro Leu Gln Gly
35 40 45

Tyr Thr Gln Val Leu Val Lys Trp Leu Val Gln Arg Gly Ser Asp Pro
50 55 60

Val Thr Ile Phe Leu Arg Asp Ser Ser Gly Asp His Ile Gln Gln Ala
65 70 75 80

Lys Tyr Gln Gly Arg Leu His Val Ser His Lys Val Pro Gly Asp Val
85 90 95

Ser Leu Gln Leu Ser Thr Leu Glu Met Asp Asp Arg Ser His Tyr Thr
100 105 110

Cys Glu Val Thr Trp Gln Thr Pro Asp Gly Asn Gln Val Val Arg Asp
115 120 125

Lys Ile Thr Glu Leu Arg Val Gln Lys Leu Ser Val Ser Lys Pro Thr
130 135 140

Val Thr Thr Gly Ser Gly Tyr Gly Phe Thr Val Pro Gln Gly Met Arg
145 150 155 160

Ile Ser Leu Gln Cys Gln Ala Arg Gly Ser Pro Pro Ile Ser Tyr Ile
165 170 175

Trp Tyr Lys Gln Gln Thr Asn Asn Gln Glu Pro Ile Lys Val Ala Thr
180 185 190

Leu Ser Thr Leu Leu Phe Lys Pro Ala Val Ile Ala Asp Ser Gly Ser
195 200 205

Tyr Phe Cys Thr Ala Lys Gly Gln Val Gly Ser Glu Gln His Ser Asp
210 215 220

Ile Val Lys Phe Val Val Lys Asp Ser Ser Lys Leu Leu Lys Thr Lys
225 230 235 240

Thr Glu Ala Pro Thr Thr Met Thr Tyr Pro Leu Lys Ala Thr Ser Thr
245 250 255

Val Lys Gln Ser Trp Asp Trp Thr Thr Asp Met Asp Gly Tyr Leu Gly
260 265 270

Glu Thr Ser Ala Gly Pro Gly Lys Ser Leu Pro Val Phe Ala Ile Ile
275 280 285

Leu Ile Ile Ser Leu Cys Cys Met Val Val Phe Thr Met Ala Tyr Ile
290 295 300

Met Leu Cys Arg Lys Thr Ser Gln Gln Glu His Val Tyr Glu Ala Ala
305 310 315 320

Arg Ala His Ala Arg Glu Ala Asn Asp Ser Gly Glu Thr Met Arg Val
325 330 335

Ala Ile Phe Ala Ser Gly Cys Ser Ser Asp Glu Pro Thr Ser Gln Asn
340 345 350

Leu Gly Asn Asn Tyr Ser Asp Glu Pro Cys Ile Gly Gln Glu Tyr Gln
355 360 365

Ile Ile Ala Gln Ile Asn Gly Asn Tyr Ala Arg Leu Leu Asp Thr Val
370 375 380

Pro Leu Asp Tyr Glu Phe Leu Ala Thr Glu Gly Lys Ser Val Cys
385 390 395

<210> 447
<211> 223
<212> PRT
<213> Homo sapiens

<400> 447
Met Lys Phe Val Pro Cys Leu Leu Leu Val Thr Leu Ser Cys Leu Gly
1 5 10 15

Thr Leu Gly Gln Ala Pro Arg Gln Lys Gln Gly Ser Thr Gly Glu Glu
20 25 30

Phe His Phe Gln Thr Gly Gly Arg Asp Ser Cys Thr Met Arg Pro Ser
35 40 45

Ser Leu Gly Gln Gly Ala Gly Glu Val Trp Leu Arg Val Asp Cys Arg
50 55 60

Asn Thr Asp Gln Thr Tyr Trp Cys Glu Tyr Arg Gly Gln Pro Ser Met
65 70 75 80

Cys Gln Ala Phe Ala Ala Asp Pro Lys Ser Tyr Trp Asn Gln Ala Leu
85 90 95

Gln Glu Leu Arg Arg Leu His His Ala Cys Gln Gly Ala Pro Val Leu
100 105 110

Arg Pro Ser Val Cys Arg Glu Ala Gly Pro Gln Ala His Met Gln Gln
115 120 125

Val Thr Ser Ser Leu Lys Gly Ser Pro Glu Pro Asn Gln Gln Pro Glu
130 135 140

Ala Gly Thr Pro Ser Leu Arg Pro Lys Ala Thr Val Lys Leu Thr Glu
145 150 155 160

Ala Thr Gln Leu Gly Lys Asp Ser Met Glu Glu Leu Gly Lys Ala Lys
165 170 175

Pro Thr Thr Arg Pro Thr Ala Lys Pro Thr Gln Pro Gly Pro Arg Pro
180 185 190

Gly Gly Asn Glu Glu Ala Lys Lys Lys Ala Trp Glu His Cys Trp Lys
195 200 205

Pro Phe Gln Ala Leu Cys Ala Phe Leu Ile Ser Phe Phe Arg Gly
210 215 220

<210> 448
<211> 135
<212> PRT
<213> Homo sapiens

<400> 448
Met Gly Leu Trp Leu Gly Met Leu Ala Cys Val Phe Leu Ala Thr Ala
1 5 10 15

Ala Phe Val Ala Tyr Thr Ala Arg Leu Asp Trp Lys Leu Ala Ala Glu
20 25 30

Glu Ala Lys Lys His Ser Gly Arg Gln Gln Gln Gln Arg Ala Glu Ser
35 40 45

Thr Ala Thr Arg Pro Gly Pro Glu Lys Ala Val Leu Ser Ser Val Ala
50 55 60

Thr Gly Ser Ser Pro Gly Ile Thr Leu Thr Thr Tyr Ser Arg Ser Glu
65 70 75 80

Cys His Val Asp Phe Phe Arg Thr Pro Glu Glu Ala His Ala Leu Ser
85 90 95

Ala Pro Thr Ser Arg Leu Ser Val Lys Gln Leu Val Ile Arg Arg Gly
100 105 110

Ala Ala Leu Gly Ala Ala Ser Ala Thr Leu Met Val Gly Leu Thr Val
115 120 125

Arg Ile Leu Ala Thr Arg His
130 135

<210> 449
<211> 181
<212> PRT
<213> Homo sapiens

<400> 449
Met Thr Val Ile Leu Ile Ile Leu Ile Val Val Met Ala Arg Tyr Cys
1 5 10 15

Arg Ser Lys Asn Lys Asn Gly Tyr Glu Ala Gly Lys Lys Asp His Glu
20 25 30

Asp Phe Phe Thr Pro Gln Gln His Asp Lys Ser Lys Lys Pro Lys Lys
35 40 45

Asp Lys Lys Asn Lys Lys Ser Lys Gln Pro Leu Tyr Ser Ser Ile Val
50 55 60

Thr Val Glu Ala Ser Lys Pro Asn Gly Gln Arg Tyr Asp Ser Val Asn
65 70 75 80

Glu Lys Leu Ser Asp Ser Pro Ser Met Gly Arg Tyr Arg Ser Val Asn
85 90 95

Gly Gly Pro Gly Ser Pro Asp Leu Ala Arg His Tyr Lys Ser Ser Ser
100 105 110

Pro Leu Pro Thr Val Gln Leu His Pro Gln Ser Pro Thr Ala Gly Lys
115 120 125

Lys His Gln Ala Val Gln Asp Leu Pro Pro Ala Asn Thr Phe Val Gly
130 135 140

Ala Gly Asp Asn Ile Ser Ile Gly Ser Asp His Cys Ser Glu Tyr Ser
145 150 155 160

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Cys Gln Thr Asn Asn Lys Tyr Ser Lys Gln Met Arg Leu His Pro Tyr
                165                 170                 175

Ile Thr Val Phe Gly
            180



<210> 450
<211> 58
<212> PRT
<213> Homo sapiens

<400> 450
Met Arg Thr Phe Leu Thr Phe Val Ile Leu Lys Val Ile Leu Ile Phe
1               5                   10                  15

Leu Ser Ser Cys Ala Ser Phe Thr Arg Asn Leu Leu Thr Trp Pro Asn
            20                  25                  30

Asp Val Ser Thr Glu Gln Phe Glu Thr Arg Pro Phe Gly Ser Glu Leu
        35                  40                  45

Leu Gln Thr Val Ile Asn Val Ser Arg Thr
    50                  55



<210> 451
<211> 950
<212> PRT
<213> Homo sapiens

<400> 451
Met Thr Trp Arg Met Gly Pro Arg Phe Thr Met Leu Leu Ala Met Trp
1               5                   10                  15

Leu Val Cys Gly Ser Glu Pro His Pro His Ala Thr Ile Arg Gly Ser
            20                  25                  30

His Gly Gly Arg Lys Val Pro Leu Val Ser Pro Asp Ser Ser Arg Pro
        35                  40                  45

Ala Arg Phe Leu Arg His Thr Gly Arg Ser Arg Gly Ile Glu Arg Ser
    50                  55                  60

Thr Leu Glu Glu Pro Asn Leu Gln Pro Leu Gln Arg Arg Arg Ser Val
65                  70                  75                  80

Pro Val Leu Arg Leu Ala Arg Pro Thr Glu Pro Pro Ala Arg Ser Asp
                85                  90                  95

Ile Asn Gly Ala Ala Val Arg Pro Glu Gln Arg Pro Ala Ala Arg Gly
            100                 105                 110

Ser Pro Arg Glu Met Ile Arg Asp Glu Gly Ser Ser Ala Arg Ser Arg
        115                 120                 125

Met Leu Arg Phe Pro Ser Gly Ser Ser Ser Pro Asn Ile Leu Ala Ser
    130                 135                 140
```

Phe Ala Gly Lys Asn Arg Val Trp Val Ile Ser Ala Pro His Ala Ser
145 150 155 160

Glu Gly Tyr Tyr Arg Leu Met Met Ser Leu Leu Lys Asp Asp Val Tyr
165 170 175

Cys Glu Leu Ala Glu Arg His Ile Gln Gln Ile Val Leu Phe His Gln
180 185 190

Ala Gly Glu Glu Gly Gly Lys Val Arg Arg Ile Thr Ser Glu Gly Gln
195 200 205

Ile Leu Glu Gln Pro Leu Asp Pro Ser Leu Ile Pro Lys Leu Met Ser
210 215 220

Phe Leu Lys Leu Glu Lys Gly Lys Phe Gly Met Val Leu Leu Lys Lys
225 230 235 240

Thr Leu Gln Val Glu Glu Arg Tyr Pro Tyr Pro Val Arg Leu Glu Ala
245 250 255

Met Tyr Glu Val Ile Asp Gln Gly Pro Ile Arg Arg Ile Glu Lys Ile
260 265 270

Arg Gln Lys Gly Phe Val Gln Lys Cys Lys Ala Ser Gly Val Glu Gly
275 280 285

Gln Val Val Ala Glu Gly Asn Asp Gly Gly Gly Gly Ala Gly Arg Pro
290 295 300

Ser Leu Gly Ser Glu Lys Lys Lys Glu Asp Pro Arg Arg Ala Gln Val
305 310 315 320

Pro Pro Thr Arg Glu Ser Arg Val Lys Val Leu Arg Lys Leu Ala Ala
325 330 335

Thr Ala Pro Ala Leu Pro Gln Pro Pro Ser Thr Pro Arg Ala Thr Thr
340 345 350

Leu Pro Pro Ala Pro Ala Thr Thr Val Thr Arg Ser Thr Ser Arg Ala
355 360 365

Val Thr Val Ala Ala Arg Pro Met Thr Thr Thr Ala Phe Pro Thr Thr
370 375 380

Gln Arg Pro Trp Thr Pro Ser Pro Ser His Arg Pro Pro Thr Thr Thr
385 390 395 400

Glu Val Ile Thr Ala Arg Arg Pro Ser Val Ser Glu Asn Leu Tyr Pro
405 410 415

Pro Ser Arg Lys Asp Gln His Arg Glu Arg Pro Gln Thr Thr Arg Arg
420 425 430

Pro Ser Lys Ala Thr Ser Leu Glu Ser Phe Thr Asn Ala Pro Pro Thr
435 440 445

Thr Ile Ser Glu Pro Ser Thr Arg Ala Ala Gly Pro Gly Arg Phe Arg
450 455 460

Asp Asn Arg Met Asp Arg Arg Glu His Gly His Arg Asp Pro Asn Val
465 470 475 480

Val Pro Gly Pro Pro Lys Pro Ala Lys Glu Lys Pro Pro Lys Lys Lys
485 490 495

Ala Gln Asp Lys Ile Leu Ser Asn Glu Tyr Glu Glu Lys Tyr Asp Leu
500 505 510

Ser Arg Pro Thr Ala Ser Gln Leu Glu Asp Glu Leu Gln Val Gly Asn
515 520 525

Val Pro Leu Lys Lys Ala Lys Glu Ser Lys Lys His Glu Lys Leu Glu
530 535 540

Lys Pro Glu Lys Glu Lys Lys Lys Lys Met Lys Asn Glu Asn Ala Asp
545 550 555 560

Lys Leu Leu Lys Ser Glu Lys Gln Met Lys Lys Ser Glu Lys Lys Ser
565 570 575

Lys Gln Glu Lys Glu Lys Ser Lys Lys Lys Lys Gly Gly Lys Thr Glu
580 585 590

Gln Asp Gly Tyr Gln Lys Pro Thr Asn Lys His Phe Thr Gln Ser Pro
595 600 605

Lys Lys Ser Val Ala Asp Leu Leu Gly Ser Phe Glu Gly Lys Arg Arg
610 615 620

Leu Leu Leu Ile Thr Ala Pro Lys Ala Glu Asn Asn Met Tyr Val Gln
625 630 635 640

Gln Arg Asp Glu Tyr Leu Glu Ser Phe Cys Lys Met Ala Thr Arg Lys
645 650 655

Ile Ser Val Ile Thr Ile Phe Gly Pro Val Asn Asn Ser Thr Met Lys
660 665 670

Ile Asp His Phe Gln Leu Asp Asn Glu Lys Pro Met Arg Val Val Asp
675 680 685

Asp Glu Asp Leu Val Asp Gln Arg Leu Ile Ser Glu Leu Arg Lys Glu
690 695 700

Tyr Gly Met Thr Tyr Asn Asp Phe Phe Met Val Leu Thr Asp Val Asp
705 710 715 720

Leu Arg Val Lys Gln Tyr Tyr Glu Val Pro Ile Thr Met Lys Ser Val
725 730 735

Phe Asp Leu Ile Asp Thr Phe Gln Ser Arg Ile Lys Asp Met Glu Lys
740 745 750

Gln Lys Lys Glu Gly Ile Val Cys Lys Glu Asp Lys Lys Gln Ser Leu
755 760 765

Glu Asn Phe Leu Ser Arg Phe Arg Trp Arg Arg Arg Leu Leu Val Ile
770 775 780

Ser Ala Pro Asn Asp Glu Asp Trp Ala Tyr Ser Gln Gln Leu Ser Ala

785 790 795 800

Leu Ser Gly Gln Ala Cys Asn Phe Gly Leu Arg His Ile Thr Ile Leu
805 810 815

Lys Leu Leu Gly Val Gly Glu Glu Val Gly Gly Val Leu Glu Leu Phe
820 825 830

Pro Ile Asn Gly Ser Ser Val Val Glu Arg Glu Asp Val Pro Ala His
835 840 845

Leu Val Lys Asp Ile Arg Asn Tyr Phe Gln Val Ser Pro Glu Tyr Phe
850 855 860

Ser Met Leu Leu Val Gly Lys Asp Gly Asn Val Lys Ser Trp Tyr Pro
865 870 875 880

Ser Pro Met Trp Ser Met Val Ile Val Tyr Asp Leu Ile Asp Ser Met
885 890 895

Gln Leu Arg Arg Gln Glu Met Ala Ile Gln Gln Ser Leu Gly Met Arg
900 905 910

Cys Pro Glu Asp Glu Tyr Ala Gly Tyr Gly Tyr His Ser Tyr His Gln
915 920 925

Gly Tyr Gln Asp Gly Tyr Gln Asp Asp Tyr Arg His His Glu Ser Tyr
930 935 940

His His Gly Tyr Pro Tyr
945 950

<210> 452
<211> 260
<212> PRT
<213> Homo sapiens

<400> 452
Met Leu Ala Leu Leu Gly Leu Ser Gln Ala Leu Asn Ile Leu Leu Gly
1 5 10 15

Leu Lys Gly Leu Ala Pro Ala Glu Ile Ser Ala Val Cys Glu Lys Gly
20 25 30

Asn Phe Asn Val Ala His Gly Leu Ala Trp Ser Tyr Tyr Ile Gly Tyr
35 40 45

Leu Arg Leu Ile Leu Pro Glu Leu Gln Ala Arg Ile Arg Thr Tyr Asn
50 55 60

Gln His Tyr Asn Asn Leu Leu Arg Gly Ala Val Ser Gln Arg Leu Tyr
65 70 75 80

Ile Leu Leu Pro Leu Asp Cys Gly Val Pro Asp Asn Leu Ser Met Ala
85 90 95

Asp Pro Asn Ile Arg Phe Leu Asp Lys Leu Pro Gln Gln Thr Gly Asp
100 105 110

Arg Ala Gly Ile Lys Asp Arg Val Tyr Ser Asn Ser Ile Tyr Glu Leu
115 120 125

Leu Glu Asn Gly Gln Arg Ala Gly Thr Cys Val Leu Glu Tyr Ala Thr
130 135 140

Pro Leu Gln Thr Leu Phe Ala Met Ser Gln Tyr Ser Gln Ala Gly Phe
145 150 155 160

Ser Gly Glu Asp Arg Leu Glu Gln Ala Lys Leu Phe Cys Arg Thr Leu
165 170 175

Glu Asp Ile Leu Ala Asp Ala Pro Glu Ser Gln Asn Asn Cys Arg Leu
180 185 190

Ile Ala Tyr Gln Glu Pro Ala Asp Asp Ser Ser Phe Ser Leu Ser Gln
195 200 205

Glu Val Leu Arg His Leu Arg Gln Glu Glu Lys Glu Glu Val Thr Val
210 215 220

Gly Ser Leu Lys Thr Ser Ala Val Pro Ser Thr Ser Thr Met Ser Gln
225 230 235 240

Glu Pro Glu Leu Leu Ile Ser Gly Met Glu Lys Pro Leu Pro Leu Arg
245 250 255

Thr Asp Phe Ser
260

<210> 453
<211> 35
<212> PRT
<213> Homo sapiens

<400> 453
Met Pro Leu Pro Ser Ser Phe Pro Leu Pro Val Phe Leu Ser Ser Cys
1 5 10 15

Pro Phe Leu Met Ser Val Ser Ile Gly Phe Leu Ile Leu Val Phe Asn
20 25 30

Val His Pro
35

<210> 454
<211> 55
<212> PRT
<213> Homo sapiens

<400> 454
Met Val Asn Ile Phe Gly Phe Val Ser Cys Ile Val Phe Arg Cys Ser
1 5 10 15

Cys Ser Ala Leu Leu His Glu Ser Asn His Arg Pro Tyr Leu Asn Lys
20 25 30

Trp Ser Leu Leu Ser Thr Asn Lys Thr Leu Phe Arg Asn Asn Arg Gly
35 40 45

Leu Asp Leu Val Leu Val Cys
50 55

<210> 455
<211> 78
<212> PRT
<213> Homo sapiens

<400> 455
Met Val Cys Phe Gln Ser Asn Lys Pro Ser Thr Ser Thr Trp Arg Gln
1 5 10 15

Leu Ser Phe Val Phe Val Leu Phe Cys Leu Phe Cys Leu Gly His Ala
20 25 30

Phe Leu Ser Leu Pro Phe Tyr Ile Leu Ser Ile Ile Ala Met Cys Leu
35 40 45

Glu Gln Trp Ala Phe His Asn Met Asn Ser Leu Tyr His His Glu Trp
50 55 60

Glu Val Arg Gly Asn Leu Ile His Val Asp Phe Thr Leu Pro
65 70 75

<210> 456
<211> 41
<212> PRT
<213> Homo sapiens

<400> 456
Met Asn Leu Met Val Arg Leu Leu Ala Leu Gly Leu Ile Ser Gly Met
1 5 10 15

Met Ser Asn Ile Thr Gln Ser His Ser Ser Lys Ile Ser Ala Phe Gly
20 25 30

Ile Phe Ile Gly Pro Glu Gln Phe Leu
35 40

<210> 457
<211> 56
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (32)
<223> Xaa equals any amino acid

<400> 457
Met Leu Ser Phe Phe Ile Cys Leu Leu Ile Phe Val His Leu Leu Leu
1 5 10 15

Leu Ser Phe Leu Ile Ser Asp Trp Pro Pro Pro Thr Gly Ser Ala Xaa
20 25 30

His Lys Ile Leu Arg Leu Met Val Val Gln Arg Leu Ser Leu Leu Asp
35 40 45

Gln Arg Lys Arg Trp Ser Glu Ala
50 55

<210> 458
<211> 90
<212> PRT
<213> Homo sapiens

<400> 458
Met Ala Ile Arg Leu Val Phe Leu Ala Leu Ala Gly Leu Val Asp Gly
1 5 10 15

Lys Pro Val Trp Ile Thr Leu Trp Met Asp Ala Lys Arg Pro Asn Leu
20 25 30

Ala Gly Thr Gly Ser Thr Trp Gly Ser Arg Arg Asp Ser His Cys Cys
35 40 45

His Gly Pro Thr Ala Trp Ser Leu Pro Cys Leu Leu Cys Leu Phe Arg
50 55 60

Ala Gln Gln Lys Asp Arg Glu Arg Ser Leu Leu Gly Val Pro Leu Pro
65 70 75 80

Thr Leu Gln Gly Gly Asn Leu Ser Asp Gly
85 90

<210> 459
<211> 282
<212> PRT
<213> Homo sapiens

<400> 459
Met Leu Ala Leu Thr Leu Ala Lys Ala Asp Ser Pro Arg Thr Ala Leu
1 5 10 15

Leu Cys Ser Ala Trp Leu Leu Thr Ala Ser Phe Ser Ala Gln Gln His
20 25 30

Lys Gly Ser Leu Gln Val His Gln Thr Leu Ser Val Glu Met Asp Gln
35 40 45

Val Leu Lys Ala Leu Ser Phe Pro Lys Lys Lys Ala Ala Leu Leu Ser
50 55 60

Ala Ala Ile Leu Cys Phe Leu Arg Thr Ala Leu Arg Gln Ser Phe Ser
65 70 75 80

Ser Ala Leu Val Ala Leu Val Pro Ser Gly Ala Gln Pro Leu Pro Ala
85 90 95

```
Thr Lys Asp Thr Val Leu Ala Pro Leu Arg Met Ser Gln Val Arg Ser
            100                 105                 110

Leu Val Ile Gly Leu Gln Asn Leu Leu Val Gln Lys Asp Pro Leu Leu
        115                 120                 125

Ser Gln Ala Cys Val Gly Cys Leu Glu Ala Leu Leu Asp Tyr Leu Asp
    130                 135                 140

Ala Arg Ser Pro Asp Ile Ala Leu His Val Ala Ser Gln Pro Trp Asn
145                 150                 155                 160

Arg Phe Leu Leu Phe Thr Leu Leu Asp Ala Gly Glu Asn Ser Phe Leu
                165                 170                 175

Arg Pro Glu Ile Leu Arg Leu Met Thr Leu Phe Met Arg Tyr Arg Ser
            180                 185                 190

Ser Ser Val Leu Ser His Glu Glu Val Gly Asp Val Leu Gln Gly Val
        195                 200                 205

Ala Leu Ala Asp Leu Ser Thr Leu Ser Asn Thr Thr Leu Gln Ala Leu
    210                 215                 220

His Gly Phe Phe Gln Gln Leu Gln Ser Met Gly His Leu Ala Asp His
225                 230                 235                 240

Ser Met Ala Gln Thr Leu Gln Ala Ser Leu Glu Gly Leu Pro Pro Ser
                245                 250                 255

Thr Ser Ser Gly Gln Pro Pro Leu Gln Asp Met Leu Cys Leu Gly Gly
            260                 265                 270

Val Ala Val Ser Leu Ser His Ile Arg Asn
        275                 280


<210> 460
<211> 178
<212> PRT
<213> Homo sapiens

<400> 460
Met Leu Pro Leu Leu Ile Ile Cys Leu Leu Pro Ala Ile Glu Gly Lys
 1               5                  10                  15

Asn Cys Leu Arg Cys Trp Pro Glu Leu Ser Ala Leu Ile Asp Tyr Asp
            20                  25                  30

Leu Gln Ile Leu Trp Val Thr Pro Gly Pro Pro Thr Glu Leu Ser Gln
        35                  40                  45

Ser Ile His Ser Leu Phe Leu Glu Asp Asn Asn Phe Leu Lys Pro Trp
    50                  55                  60

Tyr Leu Asp Arg Asp His Leu Glu Glu Glu Thr Ala Lys Phe Phe Thr
65                  70                  75                  80

Gln Val His Gln Ala Ile Lys Thr Leu Arg Asp Asp Lys Thr Val Leu
```

85 90 95

Leu Glu Glu Ile Tyr Thr His Lys Asn Leu Phe Thr Glu Arg Leu Asn
100 105 110

Lys Ile Ser Asp Gly Leu Lys Glu Lys Gly Ala Pro Pro Leu Ser Met
115 120 125

Asn Ala Phe Pro Ala Pro Ser Pro Thr Cys Thr Pro Glu Pro Leu Gly
130 135 140

Ser Val Cys Leu Pro Ser Thr Ser Val Ser Leu Pro Ser His Pro Pro
145 150 155 160

Trp Gln Pro Ala Met Ser Pro Val Pro Gly Thr Gly Gly Pro Pro Cys
165 170 175

Gly Leu

<210> 461
<211> 298
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (42)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (58)
<223> Xaa equals any amino acid

<400> 461
Met Ala Arg Arg Ser Arg His Arg Leu Leu Leu Leu Leu Leu Arg Tyr
1 5 10 15

Leu Val Val Ala Leu Gly Tyr His Lys Ala Tyr Gly Phe Ser Ala Pro
20 25 30

Lys Asp Gln Gln Val Val Thr Ala Val Xaa Tyr Gln Glu Ala Ile Leu
35 40 45

Ala Cys Lys Thr Pro Lys Lys Thr Val Xaa Ser Arg Leu Glu Trp Lys
50 55 60

Lys Leu Gly Arg Ser Val Ser Phe Val Tyr Tyr Gln Gln Thr Leu Gln
65 70 75 80

Gly Asp Phe Lys Asn Arg Ala Glu Met Ile Asp Phe Asn Ile Arg Ile
85 90 95

Lys Asn Val Thr Arg Ser Asp Ala Gly Lys Tyr Arg Cys Glu Val Ser
100 105 110

Ala Pro Ser Glu Gln Gly Gln Asn Leu Glu Glu Asp Thr Val Thr Leu
115 120 125

Glu Val Leu Val Ala Pro Ala Val Pro Ser Cys Glu Val Pro Ser Ser
130 135 140

Ala Leu Ser Gly Thr Val Val Glu Leu Arg Cys Gln Asp Lys Glu Gly
145 150 155 160

Asn Pro Ala Pro Glu Tyr Thr Trp Phe Lys Asp Gly Ile Arg Leu Leu
165 170 175

Glu Asn Pro Arg Leu Gly Ser Gln Ser Thr Asn Ser Ser Tyr Thr Met
180 185 190

Asn Thr Lys Thr Gly Thr Leu Gln Phe Asn Thr Val Ser Lys Leu Asp
195 200 205

Thr Gly Glu Tyr Ser Cys Glu Ala Arg Asn Ser Val Gly Tyr Arg Arg
210 215 220

Cys Pro Gly Lys Arg Met Gln Val Asp Asp Leu Asn Ile Ser Gly Ile
225 230 235 240

Ile Ala Ala Val Val Val Val Ala Leu Val Ile Ser Val Cys Gly Leu
245 250 255

Gly Val Cys Tyr Ala Gln Arg Lys Gly Tyr Phe Ser Lys Glu Thr Ser
260 265 270

Phe Gln Lys Ser Asn Ser Ser Ser Lys Ala Thr Thr Met Ser Glu Asn
275 280 285

Asp Phe Lys His Thr Lys Ser Phe Ile Ile
290 295

<210> 462
<211> 46
<212> PRT
<213> Homo sapiens

<400> 462
Met Glu Pro Val Ala Leu Leu Gln Pro Thr Trp Trp Leu Leu Asn Val
1 5 10 15

Thr Leu Pro Leu Val Ala Trp Ser Gly Pro Leu Ile Cys Arg Pro Leu
20 25 30

Leu His Gly Glu Gly Arg Gln Gly Ala Ala Cys Leu Gln Gly
35 40 45

<210> 463
<211> 44
<212> PRT
<213> Homo sapiens

<400> 463
Met Gly Trp Leu Trp Leu Glu Leu Leu Gly Leu Ser Ile Glu Glu Thr
1 5 10 15

Leu Val Trp Ala Phe Leu Asn Lys Phe Leu Asp Ser Ser Ala Ala Leu
20 25 30

Leu Trp Arg Ile Leu Gly Lys Ser Asn Leu Ser Thr
35 40

<210> 464
<211> 158
<212> PRT
<213> Homo sapiens

<400> 464
Met Ala Leu Glu Val Leu Met Leu Leu Ala Val Leu Ile Trp Thr Gly
1 5 10 15

Ala Glu Asn Leu His Val Lys Ile Ser Cys Ser Leu Asp Trp Leu Met
20 25 30

Val Ser Val Ile Pro Val Ala Glu Ser Arg Asn Leu Tyr Ile Phe Ala
35 40 45

Asp Glu Leu His Leu Gly Met Gly Cys Pro Ala Asn Arg Ile His Thr
50 55 60

Tyr Val Tyr Glu Phe Ile Tyr Leu Val Arg Asp Cys Gly Ile Arg Thr
65 70 75 80

Arg Val Val Ser Glu Glu Thr Leu Leu Phe Gln Thr Glu Leu Tyr Phe
85 90 95

Thr Pro Arg Asn Ile Asp His Asp Pro Gln Glu Ile His Leu Glu Cys
100 105 110

Ser Thr Ser Arg Lys Ser Val Trp Leu Thr Pro Val Ser Thr Glu Asn
115 120 125

Glu Ile Lys Leu Asp Pro Ser Pro Phe Ile Ala Asp Phe Gln Thr Thr
130 135 140

Ala Glu Glu Leu Gly Leu Leu Ser Ser Ser Pro Asn Leu Leu
145 150 155

<210> 465
<211> 101
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (67)
<223> Xaa equals any amino acid

<400> 465
Met Glu Leu Glu Arg Cys Ser Val Val Leu Cys Ile Leu Ala Asn Leu
1 5 10 15

Ala Val Leu Arg Ala Leu Phe Leu Pro Cys Ile Ile Phe His Cys Val
20 25 30

Ser Asp Ser Arg Ser Val Asn Arg Glu Thr Lys Val Lys Phe Val His
35 40 45

Thr Ser Val His Gly Val Gly His Ser Phe Val Gln Ser Ala Phe Lys
50 55 60

Ala Phe Xaa Leu Val Pro Pro Glu Ala Val Pro Glu Gln Lys Asp Pro
65 70 75 80

Asp Pro Glu Phe Pro Thr Val Lys Tyr Pro Asn Pro Glu Glu Gly Lys
85 90 95

Gly Val Leu Val Thr
100

<210> 466
<211> 71
<212> PRT
<213> Homo sapiens

<400> 466
Met Val Gln Gly Pro Leu Thr His Leu Met Leu Val Leu Leu Ile Ser
1 5 10 15

Leu Ile Phe Leu Ser Arg Gly Ser Gly Arg Ala Trp Ala Phe Ser His
20 25 30

Ser Cys Phe Lys Thr Ser Asp Leu Leu Pro Cys Arg Asn Arg Trp Glu
35 40 45

Val Ile Glu Phe Leu His Tyr Ser Asn Leu His Ser His Ile Ser Leu
50 55 60

Ser Val Thr Lys Thr Phe Leu
65 70

<210> 467
<211> 230
<212> PRT
<213> Homo sapiens

<400> 467
Met Ala Ser Leu Gly Leu Gln Leu Val Gly Tyr Ile Leu Gly Leu Leu
1 5 10 15

Gly Leu Leu Gly Thr Leu Val Ala Met Leu Leu Pro Ser Trp Lys Thr
20 25 30

Ser Ser Tyr Val Gly Ala Ser Ile Val Thr Ala Val Gly Phe Ser Lys
35 40 45

Gly Leu Trp Met Glu Cys Ala Thr His Ser Thr Gly Ile Thr Gln Cys
50 55 60

Asp Ile Tyr Ser Thr Leu Leu Gly Leu Pro Ala Asp Ile Gln Ala Ala
65 70 75 80

Gln Ala Met Met Val Thr Ser Ser Ala Ile Ser Ser Leu Ala Cys Ile
85 90 95

Ile Ser Val Val Gly Met Arg Cys Thr Val Phe Cys Gln Glu Ser Arg
100 105 110

Ala Lys Asp Arg Val Ala Val Ala Gly Gly Val Phe Phe Ile Leu Gly
115 120 125

Gly Leu Leu Gly Phe Ile Pro Val Ala Trp Asn Leu His Gly Ile Leu
130 135 140

Arg Asp Phe Tyr Ser Pro Leu Val Pro Asp Ser Met Lys Phe Glu Ile
145 150 155 160

Gly Glu Ala Leu Tyr Leu Gly Ile Ile Ser Ser Leu Phe Ser Leu Ile
165 170 175

Ala Gly Ile Ile Leu Cys Phe Ser Cys Ser Ser Gln Arg Asn Arg Ser
180 185 190

Asn Tyr Tyr Asp Ala Tyr Gln Ala Gln Pro Leu Ala Thr Arg Ser Ser
195 200 205

Pro Arg Pro Gly Gln Pro Pro Lys Val Lys Ser Glu Phe Asn Ser Tyr
210 215 220

Ser Leu Thr Gly Tyr Val
225 230

<210> 468
<211> 37
<212> PRT
<213> Homo sapiens

<400> 468
Met Cys Tyr Ile Pro Gly Ser Thr Gly Gly Gln Cys Trp Pro Trp Cys
1 5 10 15

Trp Cys Trp Leu Cys Arg Glu Ala Leu Glu Trp Leu Cys Gly Ala Val
20 25 30

Ser Ala Gly Pro Ala
35

<210> 469
<211> 133
<212> PRT
<213> Homo sapiens

<400> 469
Met Arg Val Pro Leu Val Leu Ser Trp Ala Phe Val Leu Val Gly Phe
1 5 10 15

```
Ser Gly Val Tyr Leu Ala Ser Glu Ser Phe Trp Phe Pro Pro Ser Leu
            20                  25                  30

Cys Asp Leu Thr Ser Pro Pro Gly Leu His Leu Trp Lys Phe Ile Arg
        35                  40                  45

Asp Leu Val Ser Met Glu Glu Leu Thr Asp Ser Ala Arg Glu Met Gly
    50                  55                  60

Tyr Trp Met Met Val Phe Ser Leu Lys Ala Met Phe Pro Val Ser Ser
65                  70                  75                  80

Gly Cys Phe Gln Glu Arg Gln Glu Thr Asn Lys Ser Leu Thr Leu Leu
                85                  90                  95

Arg Cys Ser Gln Arg Asp Thr Ser Pro Leu Met Asp Gly Gln Thr Trp
            100                 105                 110

Ala Arg Val Arg Val Thr Lys Pro Pro Thr Thr Ala Thr Ala Ala Tyr
        115                 120                 125

Asn Arg His Ile Arg
    130
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<210> 470
<211> 42
<212> PRT
<213> Homo sapiens

<400> 470
Met Phe Leu Phe Ile Thr Phe Thr Ile Leu Ala Ile Phe Ile Ile Glu
1               5                   10                  15

Pro Arg Asn Leu Arg Val Asp Leu Asn Leu Ile Lys Phe Gln Thr Ser
            20                  25                  30

Trp Pro Lys Thr Leu Val Glu Glu Gln Asn
        35                  40
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<210> 471
<211> 56
<212> PRT
<213> Homo sapiens

<400> 471
Met Phe Leu Lys Val Leu Val Phe Leu Ile Phe Phe Ser Pro Phe Ser
1               5                   10                  15

Ser Ser Leu Phe Ser Gly Glu Ala Val Arg Gly Arg Gly Ala Gly Leu
            20                  25                  30

Gly Leu Gly Ile Gly Arg Gly Trp Thr Ser Cys Leu Ser Val Leu Asn
        35                  40                  45

Gly Cys Asp Gly Ala Arg Ser His
    50                  55
```

<210> 472
<211> 52
<212> PRT
<213> Homo sapiens

<400> 472
Met Gly Pro Cys Arg Ala Ser Arg Cys Leu Ser Leu Leu Val Leu Phe
1 5 10 15

Pro Pro Gly Val Ala Gly Arg Pro Ala Pro Gly Arg Leu His Pro Val
20 25 30

Pro Thr Gly Pro Leu Pro Arg Met Tyr Ser Ala Gly Ala Arg Gly Arg
35 40 45

His Gly Ala His
50

<210> 473
<211> 50
<212> PRT
<213> Homo sapiens

<400> 473
Met Asp Gly Gly Pro Gly Ala Phe Ser Arg Ala Trp Val Leu Gln Ile
1 5 10 15

Pro Trp Leu Leu Leu Ser Gly Gly Asn Phe Ala Leu Cys Glu Pro Arg
20 25 30

Pro Cys Pro Ser Ala Gly His Pro Trp Gln Glu Ala Gly Leu Pro Ser
35 40 45

Ser Pro
50

<210> 474
<211> 45
<212> PRT
<213> Homo sapiens

<400> 474
Met Leu Val Ser Leu Ile Ile Cys Leu Leu Leu Asp Leu Leu Asn Gln
1 5 10 15

Pro Ser Leu Leu Arg Asp Leu Ile Leu Lys Gln His Thr Gly Asn Pro
20 25 30

His Leu Ser Phe Pro Leu Lys Tyr Ser His Trp Met Gly
35 40 45

<210> 475
<211> 168

<212> PRT
<213> Homo sapiens

<400> 475
Met Val Thr Phe Ile Thr Ala Thr Leu Trp Ile Ala Val Phe Ser Tyr
1 5 10 15

Ile Met Val Trp Leu Val Thr Ile Ile Gly Tyr Thr Leu Gly Ile Pro
20 25 30

Asp Val Ile Met Gly Ile Thr Phe Leu Ala Ala Gly Gln Val Ser Arg
35 40 45

Leu His Gly Gln Pro Asn Cys Gly Glu Thr Arg Pro Trp Gly His Gly
50 55 60

Ser Leu Gln His His Arg Ser Asn Val Phe Asp Ile Leu Val Gly Leu
65 70 75 80

Gly Val Pro Trp Gly Leu Gln Thr Met Val Val Asn Tyr Gly Ser Thr
85 90 95

Val Lys Ile Asn Ser Arg Gly Leu Val Tyr Ser Val Val Leu Leu Leu
100 105 110

Gly Ser Val Ala Leu Thr Val Leu Gly Ile His Leu Asn Lys Trp Arg
115 120 125

Leu Asp Arg Lys Leu Gly Val Tyr Val Leu Val Leu Tyr Ala Ile Phe
130 135 140

Leu Cys Phe Ser Ile Met Ile Glu Phe Asn Val Phe Thr Phe Val Asn
145 150 155 160

Leu Pro Met Cys Arg Glu Asp Asp
165

<210> 476
<211> 43
<212> PRT
<213> Homo sapiens

<400> 476
Met Asn Leu Ile Phe Arg Leu Pro Cys Ile Leu Leu Thr Cys Ile Tyr
1 5 10 15

Val Gln Gln Cys Val Cys Lys Tyr Ile Gly Thr Phe Leu Asn Arg Val
20 25 30

Cys Ala Met Cys Lys Gly Leu Leu Thr Val Lys
35 40

<210> 477
<211> 52
<212> PRT
<213> Homo sapiens

<400> 477
Met Lys Cys Phe Phe Leu Phe Val Val Ile Leu Ile Ile Met Lys Ser
1 5 10 15

Asn Leu Ser Asp Ile Ile Ile Ala Thr Tyr Thr Tyr Cys Ile Pro Asp
20 25 30

Tyr Phe Phe His Thr Phe Ile Phe Asn Leu Ser Val Tyr Leu Asn Ser
35 40 45

Lys Phe Ile Ser
50

<210> 478
<211> 51
<212> PRT
<213> Homo sapiens

<400> 478
Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
1 5 10 15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
20 25 30

Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Cys
35 40 45

Leu Leu Ala
50

<210> 479
<211> 118
<212> PRT
<213> Homo sapiens

<400> 479
Met Cys Tyr Leu Leu Leu Leu Leu Ile Gln Thr Ala Glu Leu Leu Ile
1 5 10 15

His Pro Gln Gly Leu Gln Ala Val Ser Asn Gly Glu Ser Ala Leu Lys
20 25 30

Gly Thr Arg Pro Thr Phe Ser Ser Pro Phe Ile Leu Val Thr Glu Gly
35 40 45

Arg Lys Glu Trp Glu Gly Val Phe Leu Ser Ser Gly Trp Lys Gly Asn
50 55 60

Thr Leu Ser Asn Tyr Tyr Ile Ser Leu Val Phe Tyr Tyr Ser Arg Ile
65 70 75 80

Leu Gln Pro Tyr Phe Tyr Cys Leu Trp Gly Lys Leu Glu Met Val Thr
85 90 95

Leu Ile Arg Ser Val Trp Arg Gly Ile Asn Gly Gly Asp Lys Ile Ser
100 105 110

Val Gly Phe Gly Lys Cys
115

<210> 480
<211> 169
<212> PRT
<213> Homo sapiens

<400> 480
Met Trp Ala Val Leu Arg Leu Ala Leu Arg Pro Cys Ala Arg Ala Ser
1 5 10 15

Pro Ala Gly Pro Arg Ala Tyr His Gly Asp Ser Val Ala Ser Leu Gly
20 25 30

Thr Gln Pro Asp Leu Gly Ser Ala Leu Tyr Gln Glu Asn Tyr Lys Gln
35 40 45

Met Lys Ala Leu Val Asn Gln Leu His Glu Arg Val Glu His Ile Lys
50 55 60

Leu Gly Gly Gly Glu Lys Ala Arg Ala Leu His Ile Ser Arg Gly Lys
65 70 75 80

Leu Leu Pro Arg Glu Arg Ile Asp Asn Leu Ile Asp Pro Gly Ser Pro
85 90 95

Phe Leu Glu Leu Ser Gln Phe Ala Gly Tyr Gln Leu Tyr Asp Asn Glu
100 105 110

Glu Val Pro Gly Gly Gly Ile Ile Thr Gly Ile Gly Arg Val Ser Gly
115 120 125

Val Glu Cys Met Ile Ile Ala Asn Asp Ala Thr Val Lys Gly Gly Ala
130 135 140

Tyr Tyr Pro Val Thr Val Lys Lys Gln Leu Arg Ala Gln Glu Ile Ala
145 150 155 160

Met Gln Thr Gly Ser Pro Ala Ser Thr
165

<210> 481
<211> 47
<212> PRT
<213> Homo sapiens

<400> 481
Met Thr Ala Gly Phe Met Gly Met Ala Val Ala Ile Ile Leu Phe Gly
1 5 10 15

Trp Ile Ile Gly Val Leu Gly Cys Cys Trp Asp Arg Gly Leu Met Gln
20 25 30

Tyr Val Ala Gly Cys Ser Ser Ser Trp Glu Gly Lys Gln Trp Asn
35 40 45

<210> 482
<211> 203
<212> PRT
<213> Homo sapiens

<400> 482
Met Gln Leu Gly Ser Val Leu Leu Thr Arg Cys Pro Phe Trp Gly Cys
1   5   10   15

Phe Ser Gln Leu Met Leu Tyr Ala Glu Arg Ala Glu Ala Arg Arg Lys
            20   25   30

Pro Asp Ile Pro Val Pro Tyr Leu Tyr Phe Asp Met Gly Ala Ala Val
        35   40   45

Leu Cys Ala Ser Phe Met Ser Phe Gly Val Lys Arg Arg Trp Phe Ala
    50   55   60

Leu Gly Ala Ala Leu Gln Leu Ala Ile Ser Thr Tyr Ala Ala Tyr Ile
65   70   75   80

Gly Gly Tyr Val His Tyr Gly Asp Trp Leu Lys Val Arg Met Tyr Ser
                85   90   95

Arg Thr Val Ala Ile Ile Gly Gly Phe Leu Val Leu Ala Ser Gly Ala
            100   105   110

Gly Glu Leu Tyr Arg Arg Lys Pro Arg Ser Arg Ser Leu Gln Ser Thr
        115   120   125

Gly Gln Val Phe Leu Gly Ile Tyr Leu Ile Cys Val Ala Tyr Ser Leu
    130   135   140

Gln His Ser Lys Glu Asp Arg Leu Ala Tyr Leu Asn His Leu Pro Gly
145   150   155   160

Gly Glu Leu Met Ile Gln Leu Phe Phe Val Leu Tyr Gly Ile Leu Ala
                165   170   175

Pro Gly Leu Ser Val Arg Leu Leu Arg Asp Pro Arg Cys Pro Asp Pro
            180   185   190

Gly Cys Thr Ala Ala Pro Cys His Ala Ala His
        195   200

<210> 483
<211> 123
<212> PRT
<213> Homo sapiens

<400> 483
Met His Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys Pro Ser
1   5   10   15

Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Val His Leu Asn Ile
            20   25   30

Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg Cys Tyr
35 40 45

Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe Gln Tyr
50 55 60

Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly Leu Thr
65 70 75 80

Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe Asp Ser
85 90 95

Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg Ala Ala
100 105 110

Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
115 120

<210> 484
<211> 23
<212> PRT
<213> Homo sapiens

<400> 484
Leu Gly Ser Leu Ser Thr Ala Pro Ser Ser Ala Leu Pro Thr Leu Gly
1 5 10 15

Ala Arg Arg Thr Arg Ser Lys
20

<210> 485
<211> 60
<212> PRT
<213> Homo sapiens

<400> 485
Met Gly Asn Cys Gln Ala Gly His Asn Leu His Leu Cys Leu Ala His
1 5 10 15

His Pro Pro Leu Val Cys Ala Thr Leu Ile Leu Leu Leu Leu Gly Leu
20 25 30

Ser Gly Leu Gly Leu Gly Ser Phe Leu Leu Thr His Arg Thr Gly Leu
35 40 45

Arg Thr Leu Thr Ser Pro Arg Thr Gly Ser Leu Phe
50 55 60

<210> 486
<211> 173
<212> PRT
<213> Homo sapiens

<400> 486

Met Glu Ala Pro Gly Pro Arg Ala Leu Arg Thr Ala Leu Cys Gly Gly
1   5   10   15

Cys Cys Cys Leu Leu Leu Cys Ala Gln Leu Ala Val Ala Gly Lys Gly
            20   25   30

Ala Arg Gly Phe Gly Arg Gly Ala Leu Ile Arg Leu Asn Ile Trp Pro
        35   40   45

Ala Val Gln Gly Ala Cys Lys Gln Leu Glu Val Cys Glu His Cys Val
    50   55   60

Glu Gly Asp Arg Ala Arg Asn Leu Ser Ser Cys Met Trp Glu Gln Cys
65   70   75   80

Arg Pro Glu Glu Pro Gly His Cys Val Ala Gln Ser Glu Val Val Lys
                85   90   95

Glu Gly Cys Ser Ile Tyr Asn Arg Ser Glu Ala Cys Pro Ala Ala His
            100   105   110

His His Pro Thr Tyr Glu Pro Lys Thr Val Thr Thr Gly Ser Pro Pro
        115   120   125

Val Pro Glu Ala His Ser Pro Gly Phe Asp Gly Ala Ser Phe Ile Gly
    130   135   140

Gly Val Val Leu Val Leu Ser Leu Gln Ala Val Ala Phe Phe Val Leu
145   150   155   160

His Phe Leu Lys Ala Lys Asp Ser Thr Tyr Gln Thr Leu
                165   170

<210> 487
<211> 210
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (139)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (187)
<223> Xaa equals any amino acid

<400> 487
Met Glu Ala Pro Gly Pro Arg Ala Leu Arg Thr Ala Leu Cys Gly Gly
1   5   10   15

Cys Cys Cys Leu Leu Leu Cys Ala Gln Leu Ala Val Ala Gly Lys Gly
            20   25   30

Ala Arg Gly Phe Gly Arg Gly Ala Leu Ile Arg Leu Asn Ile Trp Pro
        35   40   45

Ala Val Gln Gly Ala Cys Lys Gln Leu Glu Val Cys Glu His Cys Val

```
    50                  55                  60

Glu Gly Asp Arg Ala Arg Asn Leu Ser Ser Cys Met Trp Glu Gln Cys
65                  70                  75                  80

Arg Pro Glu Glu Pro Gly His Cys Val Ala Gln Ser Glu Val Val Lys
                85                  90                  95

Glu Gly Cys Ser Ile Tyr Asn Arg Ser Glu Ala Cys Pro Ala Ala His
            100                 105                 110

His His Pro Thr Tyr Glu Pro Lys Thr Val Thr Thr Gly Ser Pro Pro
        115                 120                 125

Val Pro Glu Ala His Ser Pro Gly Phe Asp Xaa Ala Ser Phe Ile Gly
    130                 135                 140

Gly Val Val Leu Val Leu Ser Leu Gln Ala Val Ala Phe Phe Val Leu
145                 150                 155                 160

Thr Ser Ser Arg Pro Arg Thr Ala Pro Thr Arg Arg Cys Glu Tyr Leu
                165                 170                 175

Ala Ser Ser Lys Tyr Leu Ser Pro Ser Ser Xaa Leu Val Pro Ala His
            180                 185                 190

Val Pro Phe Ser Thr Gln Gly Ala Val Phe Ser Thr Gly Lys Pro Ser
        195                 200                 205

Gly Arg
    210



<210> 488
<211> 105
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (70)
<223> Xaa equals any amino acid

<400> 488
Met Ile Ser Tyr Ile Val Leu Leu Ser Ile Leu Leu Trp Pro Leu Val
 1               5                  10                  15

Val Tyr His Glu Leu Ile Gln Arg Met Tyr Thr Arg Leu Glu Pro Leu
            20                  25                  30

Leu Met Gln Leu Asp Tyr Ser Met Lys Ala Glu Ala Asn Ala Leu His
        35                  40                  45

His Lys His Asp Lys Arg Lys Arg Gln Gly Lys Asn Ala Pro Pro Gly
    50                  55                  60

Gly Asp Glu Pro Leu Xaa Glu Thr Glu Ser Glu Ser Glu Ala Glu Leu
65                  70                  75                  80

Ala Gly Phe Ser Pro Val Val Asp Val Lys Lys Thr Ala Leu Ala Leu
```

85 90 95

Ala Ile Tyr Arg Leu Arg Ala Val Arg
100 105

<210> 489
<211> 89
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (24)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (75)
<223> Xaa equals any amino acid

<400> 489
Met Phe Lys Asp Tyr Pro Pro Ala Ile Lys Pro Ser Tyr Asp Val Leu
1 5 10 15

Leu Leu Leu Leu Leu Leu Val Xaa Leu Leu Gln Ala Gly Leu Asn Thr
20 25 30

Gly Thr Ala Ile Gln Cys Val Arg Phe Lys Val Ser Ala Arg Leu Gln
35 40 45

Gly Ala Ser Trp Asp Thr Gln Asn Gly Pro Gln Glu Arg Leu Ala Gly
50 55 60

Glu Val Ala Arg Ser Pro Leu Lys Glu Phe Xaa Lys Glu Lys Ala Trp
65 70 75 80

Arg Ala Val Val Val Gln Met Ala Gln
85

<210> 490
<211> 127
<212> PRT
<213> Homo sapiens

<400> 490
Met Gly Gln Val Trp Arg Val Pro Pro Leu Leu Leu Ser Val Gln Val
1 5 10 15

Phe Leu Thr Met Ala His Ala Phe His Gln Ala Pro Glu Leu Gln Trp
20 25 30

Leu Gly Leu Trp Phe Trp Val Arg Leu Phe Ala Gly Gly Asp Gly Gly
35 40 45

Leu His Leu Asn Ile Ser Ser Val Thr Leu Pro Leu Leu His Gly Lys
50 55 60

Gln Leu Ser Arg Glu Val Pro Ser Cys Gln Gly Lys Pro Arg Leu Gly
65 70 75 80

Arg Pro Pro Tyr Lys Glu Pro Gln Asp Cys Ser His Gly Cys His Leu
85 90 95

Ser Trp Lys Gly Arg Phe Met Gly Phe Pro Gly Thr Pro Arg Leu Ser
100 105 110

Trp Pro Arg Gly Lys Arg Trp Leu Leu Gln Glu Phe Asp Leu Ser
115 120 125

<210> 491
<211> 9
<212> PRT
<213> Homo sapiens

<400> 491
Leu Gly Lys Pro Trp Arg Tyr Pro Thr
1 5

<210> 492
<211> 91
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (84)
<223> Xaa equals any amino acid

<400> 492
Met Tyr Gly Lys Ser Ser Thr Arg Ala Val Leu Leu Leu Leu Gly Ile
1 5 10 15

Gln Leu Thr Ala Leu Trp Pro Ile Ala Ala Val Glu Ile Tyr Thr Ser
20 25 30

Arg Val Leu Glu Ala Val Asn Gly Thr Asp Ala Arg Leu Lys Cys Thr
35 40 45

Phe Ser Ser Phe Ala Pro Val Gly Asp Ala Leu Thr Val Thr Trp Asn
50 55 60

Phe Arg Pro Leu Asp Gly Gly Pro Glu Gln Phe Val Phe Tyr Tyr His
65 70 75 80

Ile Asp Pro Xaa Pro Thr His Glu Trp Ala Val
85 90

<210> 493
<211> 941
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (807)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (809)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (815)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (819)
<223> Xaa equals any amino acid

<400> 493
```
Met Val Phe Leu Pro Leu Lys Trp Ser Leu Ala Thr Met Ser Phe Leu
  1               5                  10                  15

Leu Ser Ser Leu Leu Ala Leu Leu Thr Val Ser Thr Pro Ser Trp Cys
             20                  25                  30

Gln Ser Thr Glu Ala Ser Pro Lys Arg Ser Asp Gly Thr Pro Phe Pro
         35                  40                  45

Trp Asn Lys Ile Arg Leu Pro Glu Tyr Val Ile Pro Val His Tyr Asp
     50                  55                  60

Leu Leu Ile His Ala Asn Leu Thr Thr Leu Thr Phe Trp Gly Thr Thr
 65                  70                  75                  80

Lys Val Glu Ile Thr Ala Ser Gln Pro Thr Ser Thr Ile Ile Leu His
                 85                  90                  95

Ser His His Leu Gln Ile Ser Arg Ala Thr Leu Arg Lys Gly Ala Gly
            100                 105                 110

Glu Arg Leu Ser Glu Glu Pro Leu Gln Val Leu Glu His Pro Pro Gln
        115                 120                 125

Glu Gln Ile Ala Leu Leu Ala Pro Glu Pro Leu Leu Val Gly Leu Pro
    130                 135                 140

Tyr Thr Val Val Ile His Tyr Ala Gly Asn Leu Ser Glu Thr Phe His
145                 150                 155                 160

Gly Phe Tyr Lys Ser Thr Tyr Arg Thr Lys Glu Gly Glu Leu Arg Ile
                165                 170                 175

Leu Ala Ser Thr Gln Phe Glu Pro Thr Ala Ala Arg Met Ala Phe Pro
            180                 185                 190

Cys Phe Asp Glu Pro Ala Phe Lys Ala Ser Phe Ser Ile Lys Ile Arg
        195                 200                 205

Arg Glu Pro Arg His Leu Ala Ile Ser Asn Met Pro Leu Val Lys Ser
```

210 215 220

Val Thr Val Ala Glu Gly Leu Ile Glu Asp His Phe Asp Val Thr Val
225 230 235 240

Lys Met Ser Thr Tyr Leu Val Ala Phe Ile Ile Ser Asp Phe Glu Ser
245 250 255

Val Ser Lys Ile Thr Lys Ser Gly Val Lys Val Ser Val Tyr Ala Val
260 265 270

Pro Asp Lys Met Asn Gln Ala Asp Tyr Ala Leu Asp Ala Ala Val Thr
275 280 285

Leu Leu Glu Phe Tyr Glu Asp Tyr Phe Ser Ile Pro Tyr Pro Leu Pro
290 295 300

Lys Gln Asp Leu Ala Ala Ile Pro Asp Phe Gln Ser Gly Ala Met Glu
305 310 315 320

Asn Trp Gly Leu Thr Thr Tyr Arg Glu Ser Ala Leu Leu Phe Asp Ala
325 330 335

Glu Lys Ser Ser Ala Ser Ser Lys Leu Gly Ile Thr Met Thr Val Ala
340 345 350

His Glu Leu Ala His Gln Trp Phe Gly Asn Leu Val Thr Met Glu Trp
355 360 365

Trp Asn Asp Leu Trp Leu Asn Glu Gly Phe Ala Lys Phe Met Glu Phe
370 375 380

Val Ser Val Ser Val Thr His Pro Glu Leu Lys Val Gly Asp Tyr Phe
385 390 395 400

Phe Gly Lys Cys Phe Asp Ala Met Glu Val Asp Ala Leu Asn Ser Ser
405 410 415

His Pro Val Ser Thr Pro Val Glu Asn Pro Ala Gln Ile Arg Glu Met
420 425 430

Phe Asp Asp Val Ser Tyr Asp Lys Gly Ala Cys Ile Leu Asn Met Leu
435 440 445

Arg Glu Tyr Leu Ser Ala Asp Ala Phe Lys Ser Gly Ile Val Gln Tyr
450 455 460

Leu Gln Lys His Ser Tyr Lys Asn Thr Lys Asn Glu Asp Leu Trp Asp
465 470 475 480

Ser Met Ala Ser Ile Cys Pro Thr Asp Gly Val Lys Gly Met Asp Gly
485 490 495

Phe Cys Ser Arg Ser Gln His Ser Ser Ser Ser Ser His Trp His Gln
500 505 510

Glu Gly Val Asp Val Lys Thr Met Met Asn Thr Trp Thr Leu Gln Arg
515 520 525

Gly Phe Pro Leu Ile Thr Ile Thr Val Arg Gly Arg Asn Val His Met
530 535 540

Lys Gln Glu His Tyr Met Lys Gly Ser Asp Gly Ala Pro Asp Thr Gly
545 550 555 560

Tyr Leu Trp His Val Pro Leu Thr Phe Ile Thr Ser Lys Ser Asp Met
565 570 575

Val His Arg Phe Leu Leu Lys Thr Lys Thr Asp Val Leu Ile Leu Pro
580 585 590

Glu Glu Val Glu Trp Ile Lys Phe Asn Val Gly Met Asn Gly Tyr Tyr
595 600 605

Ile Val His Tyr Glu Asp Asp Gly Trp Asp Ser Leu Thr Gly Leu Leu
610 615 620

Lys Gly Thr His Thr Ala Val Ser Ser Asn Asp Arg Ala Ser Leu Ile
625 630 635 640

Asn Asn Ala Phe Gln Leu Val Ser Ile Gly Lys Leu Ser Ile Glu Lys
645 650 655

Ala Leu Asp Leu Ser Leu Tyr Leu Lys His Glu Thr Glu Ile Met Pro
660 665 670

Val Phe Gln Gly Leu Asn Glu Leu Ile Pro Met Tyr Lys Leu Met Glu
675 680 685

Lys Arg Asp Met Asn Glu Val Glu Thr Gln Phe Lys Ala Phe Leu Ile
690 695 700

Arg Leu Leu Arg Asp Leu Ile Asp Lys Gln Thr Trp Thr Asp Glu Gly
705 710 715 720

Ser Val Ser Glu Arg Met Leu Arg Ser Glu Leu Leu Leu Leu Ala Cys
725 730 735

Val His Asn Tyr Gln Pro Cys Val Gln Arg Ala Glu Gly Tyr Phe Arg
740 745 750

Lys Trp Lys Glu Ser Asn Gly Asn Leu Ser Leu Pro Val Asp Val Thr
755 760 765

Leu Ala Val Phe Ala Val Gly Ala Gln Ser Thr Glu Gly Trp Asp Phe
770 775 780

Leu Tyr Ser Lys Tyr Gln Phe Ser Leu Ser Ser Thr Glu Lys Ser Gln
785 790 795 800

Ile Glu Phe Ala Leu Cys Xaa Pro Xaa Asn Lys Glu Lys Leu Xaa Trp
805 810 815

Leu Leu Xaa Glu Ser Phe Lys Gly Asp Lys Ile Lys Thr Gln Glu Phe
820 825 830

Pro Gln Ile Leu Thr Leu Ile Gly Arg Asn Pro Val Gly Tyr Pro Leu
835 840 845

Ala Trp Gln Phe Leu Arg Lys Asn Trp Asn Lys Leu Val Gln Lys Phe
850 855 860

Glu Leu Gly Ser Ser Ser Ile Ala His Met Val Met Gly Thr Thr Asn
865 870 875 880

Gln Phe Ser Thr Arg Thr Arg Leu Glu Glu Val Lys Gly Phe Phe Ser
885 890 895

Ser Leu Lys Glu Asn Gly Ser Gln Leu Arg Cys Val Gln Gln Thr Ile
900 905 910

Glu Thr Ile Glu Glu Asn Ile Gly Trp Met Asp Lys Asn Phe Asp Lys
915 920 925

Ile Arg Val Trp Leu Gln Ser Glu Lys Leu Glu Arg Met
930 935 940

<210> 494
<211> 157
<212> PRT
<213> Homo sapiens

<400> 494
Met Val Lys Ser Val Ile Phe Leu Ser Phe Trp Gln Gly Met Leu Leu
1 5 10 15

Ala Ile Leu Glu Lys Cys Gly Ala Ile Pro Lys Ile His Ser Ala Arg
20 25 30

Val Ser Val Gly Glu Gly Thr Val Ala Ala Gly Tyr His Asp Phe Ile
35 40 45

Ile Cys Val Glu Met Phe Phe Ala Ala Leu Ala Leu Arg His Pro Phe
50 55 60

Thr Tyr Asn Val Tyr Ala Asp Lys Arg Leu Asp Ala Gln Gly Arg Cys
65 70 75 80

Ala Pro Met Lys Ser Ile Ser Ser Ser Leu Lys Glu Thr Met Asn Pro
85 90 95

His Asp Ile Val Gln Asp Ala Ile His Asn Phe Ser Pro Ala Tyr Gln
100 105 110

Gln Tyr Thr Gln Gln Ser Thr Leu Glu Pro Gly Pro Thr Trp Arg Gly
115 120 125

Gly Ala His Gly Leu Ser Arg Ser His Ser Leu Ser Gly Ala Arg Asp
130 135 140

Asn Glu Lys Thr Leu Leu Leu Ser Ser Asp Asp Glu Phe
145 150 155

<210> 495
<211> 118
<212> PRT
<213> Homo sapiens

<400> 495

Phe Leu Ser Ser Trp Gln Arg Pro Ala Cys Gly Cys Gln Arg Pro Ala
1 5 10 15

Leu Pro Leu His Leu Gly Gly Ala Glu Gln Leu Gly Pro Ser Cys Pro
20 25 30

Gly Gly Trp Val Gln Thr Gln Ala Glu Asp Gln Pro Trp Pro Cys Pro
35 40 45

Ala Ile Cys Phe His Gln Ala Val Ser Pro Pro Trp Leu Pro Phe Ser
50 55 60

Leu Gln Ala Lys Val Leu Leu Ile Pro Thr Pro Leu Val Phe Ala Cys
65 70 75 80

Pro Ala Leu Leu Phe Ala Trp Arg Val Gly Gly Ala Gln Trp Gln Gly
85 90 95

Ile Ser Gly Pro Trp Gly Arg Gly Asp Gly Asn Met Cys Pro Thr Ala
100 105 110

Pro Ser Pro Pro Pro Pro
115

<210> 496
<211> 59
<212> PRT
<213> Homo sapiens

<400> 496
Met Met Lys Asp Val Phe Phe Phe Leu Phe Leu Leu Ala Val Trp Val
1 5 10 15

Val Ser Phe Gly Val Ala Lys Gln Ala Ile Leu Ile His Asn Glu Arg
20 25 30

Arg Val Asp Trp Leu Phe Arg Gly Pro Ser Thr Thr Pro Thr Ser Pro
35 40 45

Ser Ser Gly Arg Ser Arg Ala Thr Ser Thr Val
50 55

<210> 497
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (94)
<223> Xaa equals any amino acid

<400> 497
Met Asn Thr Leu Val Leu Trp Ile Phe Gly Phe Leu Ile Cys Leu Gly
1 5 10 15

Ile Ile Leu Ala Ile Gly Asn Ser Ile Trp Glu Ser Gln Thr Gly Asp

```
            20                  25                  30

Gln Phe Arg Thr Phe Leu Phe Trp Asn Glu Gly Glu Lys Ser Ser Val
        35                  40                  45

Phe Ser Gly Phe Leu Thr Phe Trp Ser Tyr Ile Ile Ile Leu Asn Thr
    50                  55                  60

Val Val Pro Ile Ser Leu Tyr Val Ser Val Glu Val Ile Arg Leu Gly
65                  70                  75                  80

His Ser Tyr Phe Ile Asn Trp Asp Arg Lys Met Tyr Tyr Xaa Arg Lys
                85                  90                  95

Ala Ile Pro Ala Val Ala Arg Thr Thr Thr Leu Asn Glu
            100                 105



<210> 498
<211> 46
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (45)
<223> Xaa equals any amino acid

<400> 498
Ile Asn His Val Phe Ile Trp Gly Ser Ile Ala Ile Tyr Phe Ser Ile
 1               5                  10                  15

Leu Phe Thr Met His Ser Asn Gly Ile Phe Gly Ile Phe Pro Asn Gln
            20                  25                  30

Phe Pro Phe Val Gly Asn Ala Arg His Ser Leu Thr Xaa Lys
        35                  40                  45



<210> 499
<211> 6
<212> PRT
<213> Homo sapiens

<400> 499
Thr Val Ala Ile Tyr Asp
 1               5



<210> 500
<211> 11
<212> PRT
<213> Homo sapiens

<400> 500
Phe Leu Val Cys Leu Leu Leu Gly Pro Arg Ser
 1               5                  10
```

<210> 501
<211> 56
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (35)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (42)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (46)
<223> Xaa equals any amino acid

<400> 501
Lys Ser Gln Met Gln Ser Phe Thr Ile Val Thr Ala Tyr Gly Arg Cys
1 5 10 15

Leu Ser Leu Thr Cys Leu Pro Thr Leu Asn Gln Met Leu Val Phe Lys
20 25 30

Ser Asn Xaa Ser Leu Val Ser Pro His Xaa Leu Thr Phe Xaa Asn Ile
35 40 45

Phe Ala Arg Phe Glu Asn Phe Gln
50 55

<210> 502
<211> 53
<212> PRT
<213> Homo sapiens

<400> 502
Asn Tyr Asn Arg Gly Gly Thr Phe Leu Tyr Gln Lys Ala Lys Ile Lys
1 5 10 15

His His Val Leu Met Val Phe Tyr Lys Ser Thr Ser Asn Ser Thr Glu
20 25 30

Ser Leu Ile Trp Ser Leu Leu Asn Ser Trp Ser Asp Lys Val Thr Phe
35 40 45

Pro Lys Arg Val Arg
50

<210> 503
<211> 46
<212> PRT
<213> Homo sapiens

<400> 503
```
Met Pro Trp Leu Lys Ser Leu Leu His Phe Ser Leu Phe Leu Val Val
 1               5                  10                  15

Phe Ser Thr Leu Ala Val Lys Ser Leu Gly Val Pro Val Ala Ala Gly
            20                  25                  30

Ser Pro Phe Cys Ile Val Asp Val Leu His Phe Ile Leu Leu
        35                  40                  45
```

<210> 504
<211> 64
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (7)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (27)
<223> Xaa equals any amino acid

<400> 504
```
Ser Trp Val Ile Val Val Xaa Ile Trp Gly Tyr Leu Leu Glu Gly His
 1               5                  10                  15

Gly Val Pro Phe Cys Lys Ser Tyr Gly Pro Xaa Pro Trp Lys Leu His
            20                  25                  30

Thr His His Ala Ala Tyr Asn Ser Gly Ser Ser Gln Val Tyr Arg Ile
        35                  40                  45

Leu Gly Asn Ser Pro Cys Pro Val Leu Ile His Cys Ser Phe Ser Gly
    50                  55                  60
```

<210> 505
<211> 14
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (9)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (14)
<223> Xaa equals any amino acid

<400> 505
Trp Lys Gly Leu Leu Glu Gly Ser Xaa Glu Ala Thr Met Xaa
1 5 10

<210> 506
<211> 107
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (66)
<223> Xaa equals any amino acid

<400> 506
Pro Leu Gly Arg Glu Pro Leu Ala Gly Phe Leu Ser Phe Leu Ser Phe
1 5 10 15

Ser Leu Leu Trp Cys Leu Glu Ala Phe Pro Arg Leu Gln Phe Leu Thr
20 25 30

Thr Leu Thr Asp Phe Ala Ile Val Leu Ser Pro Pro Leu Ser Phe Pro
35 40 45

Lys Leu Thr Leu Trp Arg Leu Ile Lys Arg Lys Asn His Arg Pro Gly
50 55 60

Ala Xaa Leu Thr Pro Arg Arg Arg Ala Asn His Leu Arg Cys Gly Val
65 70 75 80

Arg Asp Gln Pro Asp Gln Asn Arg Glu Thr Pro Ser Leu Leu Asn Asn
85 90 95

Thr Lys Leu Ala Gly Arg Gly Gly Ala Arg Leu
100 105

<210> 507
<211> 127
<212> PRT
<213> Homo sapiens

<400> 507
Met Pro Arg Ala Pro Trp Arg Ile Pro Leu Cys Ala Leu Pro Thr Leu
1 5 10 15

Cys Leu Gly Ser Pro Leu Pro Ser Gln Pro Thr His Pro Ile Phe Tyr
20 25 30

Asp His Arg Ala Pro Thr Trp Lys Met Ala His Pro Gly Gly Pro Arg
35 40 45

Ser Ser His Ser Pro Arg Gly Pro Gly Gly His Pro Ala Leu Arg Gln
50 55 60

Arg Leu Pro Cys Arg Arg Gly Glu Pro Glu Thr Ala Leu Cys Ser Ser
65 70 75 80

Ala Pro Gly Ala Gly Phe Ala Glu Pro Pro Cys Lys Ala Ser Pro Gly
85 90 95

Trp Gly Pro Pro Ser Arg Gly Pro Gln Gly Asp Arg Ser Gln Gly Glu
100 105 110

Trp Leu Pro Ala Leu Gly Thr Pro Cys Gly Gly Pro Asp Asp Ser
115 120 125

<210> 508
<211> 90
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (31)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (57)
<223> Xaa equals any amino acid

<400> 508
Met Pro Arg Ala Pro Trp Arg Ile Pro Leu Cys Ala Leu Pro Thr Leu
1 5 10 15

Cys Leu Gly Ser Pro Leu Pro Ser Gln Pro Thr His Pro Ile Xaa Tyr
20 25 30

Asp His Arg Ala Pro Thr Trp Lys Met Ala His Pro Gly Gly Pro Arg
35 40 45

Ser Ser His Ser Pro Arg Thr Trp Xaa Thr Pro Ser Ser Gln Thr Lys
50 55 60

Ala Ala Leu Pro Ala Gly Gly Ala Arg Asn Ser Pro Leu Gln Leu Cys
65 70 75 80

Thr Arg Ser Arg Phe Cys Gly Thr Pro Met
85 90

<210> 509
<211> 308
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (87)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (185)
<223> Xaa equals any amino acid

<400> 509

Met Pro Val Pro Trp Phe Leu Leu Ser Leu Ala Leu Gly Arg Ser Pro
1 5 10 15

Val Val Leu Ser Leu Glu Arg Leu Val Gly Pro Gln Asp Ala Thr His
20 25 30

Cys Ser Pro Gly Leu Ser Cys Arg Leu Trp Asp Ser Asp Ile Leu Cys
35 40 45

Leu Pro Gly Asp Ile Val Pro Ala Pro Gly Pro Val Leu Ala Pro Thr
50 55 60

His Leu Gln Thr Glu Leu Val Leu Arg Cys Gln Lys Glu Thr Asp Cys
65 70 75 80

Asp Leu Cys Leu Arg Val Xaa Val His Leu Ala Val His Gly His Trp
85 90 95

Glu Glu Pro Glu Asp Glu Glu Lys Phe Gly Gly Ala Ala Asp Leu Gly
100 105 110

Val Glu Glu Pro Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu Ser
115 120 125

Phe Gln Ala Tyr Pro Thr Ala Arg Cys Val Leu Leu Glu Val Gln Val
130 135 140

Pro Ala Ala Leu Val Gln Phe Gly Gln Ser Val Gly Ser Val Val Tyr
145 150 155 160

Asp Cys Phe Glu Ala Ala Leu Gly Ser Glu Val Arg Ile Trp Ser Tyr
165 170 175

Thr Gln Pro Arg Tyr Glu Lys Glu Xaa Asn His Thr Gln Gln Leu Pro
180 185 190

Asp Cys Arg Gly Leu Glu Val Trp Asn Ser Ile Pro Ser Cys Trp Ala
195 200 205

Leu Pro Trp Leu Asn Val Ser Ala Asp Gly Asp Asn Val His Leu Val
210 215 220

Leu Asn Val Ser Glu Glu Gln His Phe Gly Leu Ser Leu Tyr Trp Asn
225 230 235 240

Gln Val Gln Gly Pro Pro Lys Pro Arg Trp His Lys Asn Leu Thr Gly
245 250 255

Pro Gln Ile Ile Thr Leu Asn His Thr Asp Leu Val Pro Cys Leu Cys
260 265 270

Ile Gln Val Trp Pro Leu Glu Pro Asp Ser Val Arg Arg Thr Ser Ala
275 280 285

Pro Ser Gly Arg Thr Pro Ala His Thr Arg Thr Ser Gly Lys Pro Pro
290 295 300

Asp Cys Asp Cys
305

<210> 510
<211> 55
<212> PRT
<213> Homo sapiens

<400> 510
Met Ser Ser Asp Phe Leu Cys Phe Phe Phe Lys Leu Cys Asn Gln Met
1 5 10 15

Ile Leu Cys Phe Phe Phe Arg Gly Ala Glu Tyr Trp Phe Leu Leu Leu
20 25 30

Val Val Phe Ser Phe Leu Cys His Ser Cys Phe Phe Phe Val Phe Ser
35 40 45

Val Ser Asn Thr Ile Cys Ile
50 55

<210> 511
<211> 98
<212> PRT
<213> Homo sapiens

<400> 511
Met His Cys Cys Gln Leu Pro Trp Arg Cys Ala Gln Ala Pro Gln Glu
1 5 10 15

Ala Phe Leu Leu Cys Leu Leu Phe Leu Ile Leu Val Leu Val Leu Leu
20 25 30

Gly Cys Ser Arg Gly Leu Pro Gly His Thr Pro Trp Arg Leu His Pro
35 40 45

Ala Ala Ala Ala Leu Leu Ala Pro Leu Leu His Asp Ala Leu Gly Ala
50 55 60

Cys Gly Phe Gln Gly Pro Glu Tyr Leu Leu Pro Cys Leu Leu Pro Leu
65 70 75 80

Pro Lys Pro Gly Gln Leu Gln Gly Pro Trp Gly Pro Leu Trp Ala Leu
85 90 95

Leu Pro

<210> 512
<211> 22
<212> PRT
<213> Homo sapiens

<400> 512
Leu Pro Arg Pro Cys Ala Pro Ser Pro Val Trp Arg Gln Val Gly Arg
1 5 10 15

Glu Glu Ala Ser Leu Leu
20

<210> 513
<211> 25
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (9)
<223> Xaa equals any amino acid

<400> 513
Cys Ala Val Arg Phe Arg Glu Gln Xaa Ala Pro Glu Arg Val Phe Leu
1 5 10 15

Pro Thr Arg Gly Arg Lys Ser Glu Pro
20 25

<210> 514
<211> 365
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (144)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (201)
<223> Xaa equals any amino acid

<400> 514
Met Phe Val Gly Leu Met Ala Phe Leu Leu Ser Phe Tyr Leu Ile Phe
1 5 10 15

Thr Asn Glu Gly Arg Ala Leu Lys Thr Ala Thr Ser Leu Ala Glu Gly
20 25 30

Leu Ser Leu Val Val Ser Pro Asp Ser Ile His Ser Val Ala Pro Glu
35 40 45

Asn Glu Gly Arg Leu Val His Ile Ile Gly Ala Leu Arg Thr Ser Lys
50 55 60

Leu Leu Ser Asp Pro Asn Tyr Gly Val His Leu Pro Ala Val Lys Leu
65 70 75 80

Arg Arg His Val Glu Met Tyr Gln Trp Val Glu Thr Glu Glu Ser Arg
85 90 95

Glu Tyr Thr Glu Asp Gly Gln Val Lys Lys Glu Thr Arg Tyr Ser Tyr
100 105 110

Asn Thr Glu Trp Arg Ser Glu Ile Ile Asn Ser Lys Asn Phe Asp Arg
        115   120   125

Glu Ile Gly His Lys Asn Pro Ser Ala Met Ala Val Glu Ser Phe Xaa
    130   135   140

Ala Thr Ala Pro Phe Val Gln Ile Gly Arg Phe Phe Leu Ser Ser Gly
145   150   155   160

Leu Ile Asp Lys Val Asp Asn Phe Lys Ser Leu Ser Leu Ser Lys Leu
                165   170   175

Glu Asp Pro His Val Asp Ile Ile Arg Arg Gly Asp Phe Phe Tyr His
            180   185   190

Ser Glu Asn Pro Lys Tyr Pro Glu Xaa Gly Asp Leu Arg Val Ser Phe
        195   200   205

Ser Tyr Ala Gly Leu Ser Gly Asp Asp Pro Asp Leu Gly Pro Ala His
    210   215   220

Val Val Thr Val Ile Ala Arg Gln Arg Gly Asp Gln Leu Val Pro Phe
225   230   235   240

Ser Thr Lys Ser Gly Asp Thr Leu Leu Leu Leu His His Gly Asp Phe
                245   250   255

Ser Ala Glu Glu Val Phe His Arg Glu Leu Arg Ser Asn Ser Met Lys
            260   265   270

Thr Trp Gly Leu Arg Ala Ala Gly Trp Met Ala Met Phe Met Gly Leu
        275   280   285

Asn Leu Met Thr Arg Ile Leu Tyr Thr Leu Val Asp Trp Phe Pro Val
    290   295   300

Phe Arg Asp Leu Val Asn Ile Gly Leu Lys Ala Phe Ala Phe Cys Val
305   310   315   320

Ala Thr Ser Leu Thr Leu Leu Thr Val Ala Ala Gly Trp Leu Phe Tyr
                325   330   335

Arg Pro Leu Trp Ala Leu Leu Ile Ala Gly Leu Ala Leu Val Pro Ile
            340   345   350

Leu Val Ala Arg Thr Arg Val Pro Ala Lys Lys Leu Glu
        355   360   365

<210> 515
<211> 108
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (48)
<223> Xaa equals any amino acid

<220>

<221> SITE
<222> (55)
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<222> (58)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (67)
<223> Xaa equals any amino acid

<400> 515
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Met Phe Tyr Lys Leu Thr Leu Ile Leu Cys Glu Leu Ser Val Ala Gly
  1               5                  10                  15

Val Thr Gln Ala Ala Ser Gln Arg Pro Leu Gln Arg Leu Pro Arg His
             20                  25                  30

Ile Cys Ser Gln Arg Asn Pro Pro Gly Arg Cys Leu Leu Lys Ala Xaa
         35                  40                  45

Leu Gln Thr Thr Trp Gly Xaa Pro Asp Xaa Gln Phe Pro Gly Cys Pro
     50                  55                  60

His Pro Xaa Arg Val Thr Leu Asn Ala Arg Gln Met Gly Asn Gly Lys
 65                  70                  75                  80

Glu Lys Lys Ala Ala Asp Leu Lys Leu Lys Phe Pro Gln Lys Arg Phe
                 85                  90                  95

Tyr Leu Ser Ala Phe Ser Glu Arg Ile Lys Ala Phe
            100                 105
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<210> 516
<211> 73
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (38)
<223> Xaa equals any amino acid

<220>
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<222> (48)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (54)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (55)

<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (68)
<223> Xaa equals any amino acid

<400> 516
Met Phe Tyr Lys Leu Thr Leu Ile Leu Cys Glu Leu Ser Val Ala Gly
1 5 10 15

Val Thr Gln Ala Ala Ser Gln Arg Pro Leu Gln Arg Leu Pro Arg His
20 25 30

Ile Cys Ser Gln Arg Xaa Pro Pro Gly Arg Cys Leu Leu Lys Ala Xaa
35 40 45

Leu Gln Thr Thr Trp Xaa Xaa Pro Asp Lys Pro Ile Pro Arg Leu Ser
50 55 60

Pro Pro Leu Xaa Ser Asp Pro Lys Arg
65 70

<210> 517
<211> 81
<212> PRT
<213> Homo sapiens

<400> 517
Met Ser Lys Arg Ser Ala Ser Phe Ile Leu Leu Pro Leu Leu Phe Leu
1 5 10 15

Lys Gly Ser Phe Ala Lys Leu Asn Ala Arg Ile Ser Asp Cys Leu Glu
20 25 30

Glu Arg Tyr Cys His Asn Leu Trp Met Val Phe Gln Gly Cys Val Ile
35 40 45

Thr Glu Leu His Leu Ser Arg Met Ser Lys Thr Leu Ser Ser Leu Cys
50 55 60

Tyr Asp Phe Val Ile Asn Val Tyr Ile Phe Phe Lys Phe Leu Asp Ile
65 70 75 80

Thr

<210> 518
<211> 122
<212> PRT
<213> Homo sapiens

<220>
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<222> (89)
<223> Xaa equals any amino acid

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<223> Xaa equals any amino acid

<220>
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<222> (97)
<223> Xaa equals any amino acid

<220>
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<222> (98)
<223> Xaa equals any amino acid

<400> 518
Met His Arg Ser Glu Pro Phe Leu Lys Met Ser Leu Leu Ile Leu Leu
1 5 10 15

Phe Leu Gly Leu Ala Glu Ala Cys Thr Pro Arg Glu Val Asn Leu Leu
20 25 30

Lys Gly Ile Ile Gly Leu Met Ser Arg Leu Ser Pro Asp Glu Ile Leu
35 40 45

Gly Leu Leu Ser Leu Gln Val Leu His Glu Glu Thr Ser Gly Cys Lys
50 55 60

Glu Glu Val Lys Pro Phe Ser Gly Thr Thr Pro Ser Arg Lys Pro Leu
65 70 75 80

Pro Lys Arg Glu Glu His Val Glu Xaa Pro Xaa Asn Ala Xaa Thr Trp
85 90 95

Xaa Xaa Thr Tyr Leu Phe Val Ser Tyr Asn Lys Gly Asp Trp Phe Thr
100 105 110

Phe Ser Ser Gln Val Leu Leu Pro Leu Leu
115 120

<210> 519
<211> 11
<212> PRT
<213> Homo sapiens

<400> 519
Met Ser Gly Gly Leu Ser Phe Leu Leu Leu Val
1 5 10

<210> 520
<211> 130
<212> PRT

<213> Homo sapiens

<400> 520
Ser Thr Cys Cys Gly Trp Gly Pro Leu Gly His Ser Arg Val Arg Gly
1 5 10 15

Cys His Cys His Leu Gly His Val Gly Arg His Gln His Phe Val Val
20 25 30

Thr Asn Ser Thr Val Thr Asn Ile Phe Gly Gln Ile Pro Phe Tyr Thr
35 40 45

Ser Arg Gln Leu Leu Val Cys Asn Pro Thr Gly Gln Arg Glu Gly Pro
50 55 60

Val Thr Trp Leu Ser His Cys Pro Ala Pro Gln Met Val Leu Gly Leu
65 70 75 80

Leu Phe Ser Leu Gly Pro Ala Asn Thr Thr Val Phe Thr Ser Ala His
85 90 95

Trp Leu Ser Ala Val Val Pro Gly Ser Gln Trp His Val Ser Pro Arg
100 105 110

Ser Ser Leu Ile Pro Gln His Thr Pro Lys Gly Ser Val Ala Asn Thr
115 120 125

Leu Asn
130

<210> 521
<211> 122
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (19)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (73)
<223> Xaa equals any amino acid

<400> 521
Lys Ala Pro Ser Ser His Pro Gly Leu Thr Cys Val Ser Leu Ser Arg
1 5 10 15

Leu Gln Xaa Ser Leu Ser Leu Cys Phe Pro Ser Gly Pro Cys Trp Ala
20 25 30

Gly Leu Leu Ser Ser Leu Ala Leu Ala Gly Gly Ala Pro Gly Ala Leu
35 40 45

Pro Pro Trp Gln Pro Gly Gln Asp Ser Lys Met Arg Thr Ala Glu Leu
50 55 60

Val Gly Gly Ser His Gly Pro Ala Xaa Gly Pro Gly Glu Ala Glu Pro

65 70 75 80

Glu Pro Thr Ala Val Val Leu Trp Thr Val Asp Pro Glu Gly Gly Leu
85 90 95

Gly Gln Val Pro Ala Glu Gly Pro Gly Gly Leu Cys Val Pro Leu Gly
100 105 110

Pro Gly Ala Leu Val Thr Trp Thr Pro Gly
115 120

<210> 522
<211> 243
<212> PRT
<213> Homo sapiens

<400> 522
Met Gly Thr Leu Pro Trp Leu Leu Ala Phe Phe Ile Leu Gly Leu Gln
1 5 10 15

Ala Trp Asp Thr Pro Thr Ile Val Ser Arg Lys Glu Trp Gly Ala Arg
20 25 30

Pro Leu Ala Cys Arg Ala Leu Leu Thr Leu Pro Val Ala Tyr Ile Ile
35 40 45

Thr Asp Gln Leu Pro Gly Met Gln Cys Gln Gln Gln Ser Val Cys Ser
50 55 60

Gln Met Leu Arg Gly Leu Gln Ser His Ser Val Tyr Thr Ile Gly Trp
65 70 75 80

Cys Asp Val Ala Tyr Asn Phe Leu Val Gly Asp Asp Gly Arg Val Tyr
85 90 95

Glu Gly Val Gly Trp Asn Ile Gln Gly Leu His Thr Gln Gly Tyr Asn
100 105 110

Asn Ile Ser Leu Gly Ile Ala Phe Phe Gly Asn Lys Ile Ser Ser Ser
115 120 125

Pro Ser Pro Ala Ala Leu Ser Ala Ala Glu Gly Leu Ile Ser Tyr Ala
130 135 140

Ile Gln Lys Gly His Leu Ser Pro Arg Tyr Ile Gln Pro Leu Leu Leu
145 150 155 160

Lys Glu Glu Thr Cys Leu Asp Pro Gln His Pro Val Met Pro Arg Lys
165 170 175

Val Cys Pro Asn Ile Ile Lys Arg Ser Ala Trp Glu Ala Arg Glu Thr
180 185 190

His Cys Pro Lys Met Asn Leu Pro Ala Lys Tyr Val Ile Ile Ile His
195 200 205

Thr Ala Gly Thr Ser Cys Thr Val Ser Thr Asp Cys Gln Thr Val Val
210 215 220

Arg Asn Ile Gln Ser Phe His Met Asp Thr Arg Asn Phe Cys Asp Ile
225 230 235 240

Gly Tyr Gln

<210> 523
<211> 154
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (150)
<223> Xaa equals any amino acid

<400> 523
Met Ala Arg His Gly Leu Pro Leu Leu Pro Leu Leu Ser Leu Leu Val
1 5 10 15

Gly Ala Trp Leu Lys Leu Gly Asn Gly Gln Ala Thr Ser Met Val Gln
20 25 30

Leu Gln Gly Gly Arg Phe Leu Met Gly Thr Asn Ser Pro Asp Ser Arg
35 40 45

Asp Gly Glu Gly Pro Val Arg Glu Ala Thr Val Lys Pro Phe Ala Ile
50 55 60

Asp Ile Phe Pro Val Thr Asn Lys Asp Phe Arg Asp Phe Val Arg Glu
65 70 75 80

Lys Lys Tyr Arg Thr Glu Ala Glu Met Phe Gly Trp Ser Phe Val Phe
85 90 95

Glu Asp Phe Val Ser Asp Glu Leu Arg Asn Lys Ala Thr Gln Pro Met
100 105 110

Lys Ser Val Leu Trp Trp Leu Pro Val Glu Lys Ala Phe Trp Arg Gln
115 120 125

Pro Ala Gly Pro Gly Ser Gly Ile Arg Glu Arg Leu Glu His Pro Val
130 135 140

Leu His Val Ser Trp Xaa Asp Ala Arg Ala
145 150

<210> 524
<211> 57
<212> PRT
<213> Homo sapiens

<400> 524
Met Pro Cys Thr Cys Thr Trp Arg Asn Trp Arg Gln Trp Ile Arg Pro
1 5 10 15

Leu Val Ala Val Ile Tyr Leu Val Ser Ile Val Val Ala Val Pro Leu

20 25 30

Cys Val Trp Glu Leu Gln Lys Leu Glu Val Gly Ile His Thr Lys Ala
35 40 45

Trp Phe Ile Ala Gly Ile Phe Leu Leu
50 55

<210> 525
<211> 107
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (92)
<223> Xaa equals any amino acid

<400> 525
Met Val Arg Tyr Thr Tyr Ser Met Leu Ser Val Ile Gly Ile Ser Tyr
1 5 10 15

Ala Val Leu Thr Trp Leu Ser Gln Thr Leu Trp Met Pro Ile Tyr Pro
20 25 30

Leu Cys Val Leu Ala Glu Ala Phe Ala Ile Tyr Gln Ser Leu Pro Tyr
35 40 45

Phe Glu Ser Phe Gly Thr Tyr Ser Thr Lys Leu Pro Phe Asp Leu Ser
50 55 60

Ile Tyr Phe Pro Tyr Val Leu Lys Ile Tyr Leu Met Met Leu Phe Ile
65 70 75 80

Gly Met Tyr Phe Thr Tyr Ser His Leu Tyr Ser Xaa Arg Arg Asp Ile
85 90 95

Leu Gly Ile Phe Pro Ile Lys Lys Lys Lys Met
100 105

<210> 526
<211> 37
<212> PRT
<213> Homo sapiens

<400> 526
Met Val Arg Tyr Thr Tyr Ser Met Leu Ser Val Ile Gly Ile Ser Tyr
1 5 10 15

Ala Val Leu Thr Trp Ala Gln Ser Asn Thr Met Asp Ala Asn Leu Ser
20 25 30

Phe Val Cys Ser Cys
35

<210> 527
<211> 46
<212> PRT
<213> Homo sapiens

<400> 527
Met Lys Ser Gln Cys Tyr Ser Pro Ser Tyr Phe Ala Phe Phe Cys Leu
1 5 10 15

Val Phe Phe Gln Ile Thr Ser Ala Ser Ser Gln Thr Leu Arg Gly His
20 25 30

Val Leu Cys Arg Thr Thr Leu Arg Asp Ser Ser Ala Tyr Cys
35 40 45

<210> 528
<211> 442
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (364)
<223> Xaa equals any amino acid

<400> 528
Met Trp Phe Thr Tyr Leu Leu Leu Tyr Leu His Ser Val Arg Ala Tyr
1 5 10 15

Ser Ser Arg Gly Ala Gly Cys Cys Cys Cys Trp Ala Arg Trp Arg Arg
20 25 30

Ala Val His Thr Ala Arg Gly Leu Arg Gly Arg Pro Arg Arg Gln Leu
35 40 45

Leu Arg Pro Leu Arg Pro Ala Gln Gly Leu Ala Pro Gly Arg His Arg
50 55 60

Leu Arg Pro Ala Val Leu Pro Leu His Leu Gln Pro Leu Pro Gly Leu
65 70 75 80

Trp Gly Gly His Ala Glu Trp Ala Ala Leu Leu Tyr Tyr Gly Pro Phe
85 90 95

Ile Val Ile Phe Gln Phe Gly Trp Ala Ser Thr Gln Ile Ser His Leu
100 105 110

Ser Leu Ile Pro Glu Leu Val Thr Asn Asp His Glu Lys Val Glu Leu
115 120 125

Thr Ala Leu Arg Tyr Ala Phe Thr Val Val Ala Asn Ile Thr Val Tyr
130 135 140

Gly Ala Ala Trp Leu Leu Leu His Leu Gln Gly Ser Ser Arg Val Glu
145 150 155 160

Pro Thr Gln Asp Ile Ser Ile Ser Asp Gln Leu Gly Gly Gln Asp Val
165 170 175

```
Pro Val Phe Arg Asn Leu Ser Leu Leu Val Val Gly Val Gly Ala Val
            180                 185                 190

Phe Ser Leu Leu Phe His Leu Gly Thr Arg Glu Arg Arg Arg Pro His
        195                 200                 205

Ala Glu Glu Pro Gly Glu His Thr Pro Leu Leu Ala Pro Ala Thr Ala
    210                 215                 220

Gln Pro Leu Leu Leu Trp Lys His Trp Leu Arg Glu Pro Ala Phe Tyr
225                 230                 235                 240

Gln Val Gly Ile Leu Tyr Met Thr Thr Arg Leu Ile Val Asn Leu Ser
                245                 250                 255

Gln Thr Tyr Met Ala Met Tyr Leu Thr Tyr Ser Leu His Leu Pro Lys
            260                 265                 270

Lys Phe Ile Ala Thr Ile Pro Leu Val Met Tyr Leu Ser Gly Phe Leu
        275                 280                 285

Ser Ser Phe Leu Met Lys Pro Ile Asn Lys Cys Ile Gly Arg Asn Met
    290                 295                 300

Thr Tyr Phe Ser Gly Leu Leu Val Ile Leu Ala Phe Ala Ala Trp Val
305                 310                 315                 320

Ala Leu Ala Glu Gly Leu Gly Val Ala Val Tyr Ala Ala Ala Val Leu
                325                 330                 335

Leu Gly Ala Gly Cys Ala Thr Ile Leu Val Thr Ser Leu Ala Met Thr
            340                 345                 350

Ala Asp Leu Ile Gly Pro His Thr Asn Ser Gly Xaa Phe Val Tyr Gly
        355                 360                 365

Ser Met Ser Phe Leu Asp Lys Val Ala Asn Gly Leu Ala Val Met Ala
    370                 375                 380

Ile Gln Ser Leu His Pro Cys Pro Ser Glu Leu Cys Cys Arg Ala Cys
385                 390                 395                 400

Val Ser Phe Tyr His Trp Ala Met Val Ala Val Thr Gly Gly Val Gly
                405                 410                 415

Val Ala Ala Ala Leu Cys Leu Cys Ser Leu Leu Leu Trp Pro Thr Arg
            420                 425                 430

Leu Arg Arg Trp Asp Arg Asp Ala Arg Pro
        435                 440


<210> 529
<211> 309
<212> PRT
<213> Homo sapiens

<220>
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<222> (26)
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<223> Xaa equals any amino acid

<220>
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<222> (84)
<223> Xaa equals any amino acid

<220>
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<222> (111)
<223> Xaa equals any amino acid

<400> 529
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Ala Ala Asp Asn Tyr Gly Ile Pro Arg Ala Cys Arg Asn Ser Ala Arg
1               5                   10                  15

Ser Tyr Gly Ala Ala Trp Leu Leu Leu Xaa Pro Ala Gly Ser Ser Arg
            20                  25                  30

Val Glu Pro Thr Gln Asp Ile Ser Ile Ser Asp Gln Leu Gly Gly Gln
        35                  40                  45

Asp Val Pro Val Phe Arg Asn Leu Ser Leu Leu Val Val Gly Val Gly
    50                  55                  60

Ala Val Phe Ser Leu Leu Phe His Leu Gly Thr Arg Glu Arg Arg Arg
65                  70                  75                  80

Pro His Ala Xaa Glu Pro Gly Glu His Thr Pro Leu Leu Ala Pro Ala
                85                  90                  95

Thr Ala Gln Pro Leu Leu Leu Trp Lys His Trp Leu Arg Glu Xaa Ala
            100                 105                 110

Phe Tyr Gln Val Gly Ile Leu Tyr Met Thr Thr Arg Leu Ile Val Asn
        115                 120                 125

Leu Ser Gln Thr Tyr Met Ala Met Tyr Leu Thr Tyr Ser Leu His Leu
    130                 135                 140

Pro Lys Lys Phe Ile Ala Thr Ile Pro Leu Val Met Tyr Leu Ser Gly
145                 150                 155                 160

Phe Leu Ser Ser Phe Leu Met Lys Pro Ile Asn Lys Cys Ile Gly Arg
                165                 170                 175

Asn Met Thr Tyr Phe Ser Gly Leu Leu Val Ile Leu Ala Phe Ala Ala
            180                 185                 190

Trp Val Ala Leu Ala Glu Gly Leu Gly Val Ala Val Tyr Ala Ala Ala
        195                 200                 205

Val Leu Leu Gly Ala Gly Cys Ala Thr Ile Leu Val Thr Ser Leu Ala
    210                 215                 220

Met Thr Ala Asp Leu Ile Gly Pro His Thr Asn Ser Gly Ala Phe Val
225                 230                 235                 240

Tyr Gly Ser Met Ser Phe Leu Asp Lys Val Ala Asn Gly Leu Ala Val
                245                 250                 255
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Met Ala Ile Gln Ser Leu His Pro Cys Pro Ser Glu Leu Cys Cys Arg
260 265 270

Ala Cys Val Ser Phe Tyr His Trp Ala Met Val Ala Val Thr Gly Gly
275 280 285

Val Gly Val Ala Ala Ala Leu Cys Leu Cys Ser Leu Leu Leu Trp Pro
290 295 300

Thr Arg Leu Arg Arg
305

<210> 530
<211> 243
<212> PRT
<213> Homo sapiens

<220>
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<222> (26)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (84)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (111)
<223> Xaa equals any amino acid

<400> 530
Ala Ala Asp Asn Tyr Gly Ile Pro Arg Ala Cys Arg Asn Ser Ala Arg
1 5 10 15

Ser Tyr Gly Ala Ala Trp Leu Leu Leu Xaa Pro Ala Gly Ser Ser Arg
20 25 30

Val Glu Pro Thr Gln Asp Ile Ser Ile Ser Asp Gln Leu Gly Gly Gln
35 40 45

Asp Val Pro Val Phe Arg Asn Leu Ser Leu Leu Val Val Gly Val Gly
50 55 60

Ala Val Phe Ser Leu Leu Phe His Leu Gly Thr Arg Glu Arg Arg Arg
65 70 75 80

Pro His Ala Xaa Glu Pro Gly Glu His Thr Pro Leu Leu Ala Pro Ala
85 90 95

Thr Ala Gln Pro Leu Leu Leu Trp Lys His Trp Leu Arg Glu Xaa Ala
100 105 110

Phe Tyr Gln Val Gly Ile Leu Tyr Met Thr Thr Arg Leu Ile Val Asn
115 120 125

Leu Ser Gln Thr Tyr Met Ala Met Tyr Leu Thr Tyr Ser Leu His Leu
130 135 140

Pro Lys Lys Phe Ile Ala Thr Ile Pro Leu Val Met Tyr Leu Ser Gly
145 150 155 160

Phe Leu Ser Ser Phe Leu Met Lys Pro Ile Asn Lys Cys Ile Gly Arg
165 170 175

Asn Met Thr Tyr Phe Ser Gly Leu Leu Val Ile Leu Ala Phe Ala Ala
180 185 190

Trp Val Ala Leu Ala Glu Gly Leu Gly Val Ala Val Tyr Ala Ala Ala
195 200 205

Val Leu Leu Gly Ala Gly Cys Ala Thr Ile Leu Val Thr Ser Leu Ala
210 215 220

Met Thr Ala Asp Leu Ile Gly Pro His Thr Asn Ser Gly Leu Ser Cys
225 230 235 240

Thr Ala Pro

<210> 531
<211> 148
<212> PRT
<213> Homo sapiens

<400> 531
Met Ala Gly Ser Pro Leu Leu Trp Gly Pro Arg Ala Gly Gly Val Gly
1 5 10 15

Leu Leu Val Leu Leu Leu Leu Gly Leu Phe Arg Pro Pro Pro Ala Leu
20 25 30

Cys Ala Arg Pro Val Lys Glu Pro Arg Gly Leu Ser Ala Ala Ser Pro
35 40 45

Pro Leu Ala Arg Leu Ala Leu Leu Ala Ala Ser Gly Gly Gln Cys Pro
50 55 60

Glu Val Arg Arg Arg Gly Arg Cys Arg Pro Gly Ala Gly Ala Gly Ala
65 70 75 80

Ser Ala Gly Ala Glu Arg Gln Glu Arg Ala Arg Ala Glu Ala Gln Arg
85 90 95

Leu Arg Ile Ser Arg Arg Ala Ser Trp Arg Ser Cys Cys Ala Ser Gly
100 105 110

Ala Pro Pro Ala Thr Leu Ile Arg Leu Trp Ala Trp Thr Thr Thr Pro
115 120 125

Thr Arg Leu Gln Arg Ser Ser Leu Ala Leu Cys Ser Ala Pro Ala Leu
130 135 140

Thr Leu Pro Pro
145

<210> 532
<211> 65
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (24)
<223> Xaa equals any amino acid

<400> 532
Met Cys Lys Gly Leu Lys Asn Pro Glu Gly Leu Leu Leu Leu Leu Leu
1 5 10 15

Leu Leu Leu Phe Thr Asp Thr Xaa Asn Ser His Cys Leu Pro Pro Tyr
20 25 30

Leu Ser Cys Phe Leu His Glu Arg Gln Pro Glu Leu Gln Ser Val Cys
35 40 45

Ile Ser Ala Ala Tyr Val Leu Ala Pro Leu Gln Asn Pro Val Ser Ser
50 55 60

Leu
65

<210> 533
<211> 299
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (172)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (174)
<223> Xaa equals any amino acid

<400> 533
Gly Gly Glu Glu Glu Gly Glu Glu Gly Ala Glu Ile Ser Gly Leu Gly
1 5 10 15

Ala Gly Arg Arg Ser Ala Pro Ile Ala Val Gly Leu Gly Phe Leu Gly
20 25 30

Val Gly Gly Arg Gly Gly Ser Asp Met Glu Ala Asn Gly Ser Gln Gly
35 40 45

Thr Ser Gly Ser Ala Asn Asp Ser Gln His Asp Pro Gly Lys Met Phe
50 55 60

Ile Gly Gly Leu Ser Trp Gln Thr Ser Pro Asp Ser Leu Arg Asp Tyr
65 70 75 80

Phe Ser Lys Phe Gly Glu Ile Arg Glu Cys Met Val Met Arg Asp Pro

85 90 95

Thr Thr Lys Arg Ser Arg Gly Phe Gly Phe Val Thr Phe Ala Asp Pro
100 105 110

Ala Ser Val Asp Lys Val Leu Gly Gln Pro His His Glu Leu Asp Ser
115 120 125

Lys Thr Ile Asp Pro Lys Val Ala Phe Pro Arg Arg Ala Gln Pro Lys
130 135 140

Met Val Thr Arg Thr Lys Lys Ile Phe Val Gly Gly Leu Ser Ala Asn
145 150 155 160

Thr Val Val Glu Asp Val Lys Gln Tyr Phe Glu Xaa Phe Xaa Lys Val
165 170 175

Glu Asp Ala Met Leu Met Phe Asp Lys Thr Thr Asn Arg His Arg Gly
180 185 190

Phe Gly Phe Val Thr Phe Glu Asn Glu Asp Val Val Glu Lys Val Cys
195 200 205

Glu Ile His Phe His Glu Ile Asn Asn Lys Met Val Glu Cys Lys Lys
210 215 220

Ala Gln Pro Lys Glu Val Met Phe Pro Pro Gly Thr Arg Gly Arg Ala
225 230 235 240

Arg Gly Leu Pro Tyr Thr Met Asp Ala Phe Met Leu Gly Met Gly Met
245 250 255

Leu Gly Glu Ser Gly Gln Asp Arg Arg Ser Pro Trp Thr Gly Arg Ala
260 265 270

Met Glu Ala Ser Thr Pro Asn Trp Val Thr Tyr Gln Trp Gly Lys Leu
275 280 285

Leu His Leu Ser Lys Pro Gln Phe Pro Cys Leu
290 295

<210> 534
<211> 306
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (171)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (180)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (182)

<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (188)
<223> Xaa equals any amino acid

<220>
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<222> (208)
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<220>
<221> SITE
<222> (210)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (211)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (218)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (219)
<223> Xaa equals any amino acid

<400> 534
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Met Ala Leu Arg Leu Leu Arg Arg Ala Ala Arg Gly Ala Ala Ala Ala
 1               5                  10                  15

Ala Leu Leu Arg Leu Lys Ala Ser Leu Ala Ala Asp Ile Pro Arg Leu
            20                  25                  30

Gly Tyr Ser Ser Ser Ser His His Lys Tyr Ile Pro Arg Arg Ala Val
        35                  40                  45

Leu Tyr Val Pro Gly Asn Asp Glu Lys Lys Ile Lys Lys Ile Pro Ser
    50                  55                  60

Leu Asn Val Asp Cys Ala Val Leu Asp Cys Glu Asp Gly Val Ala Ala
65                  70                  75                  80

Asn Lys Lys Asn Glu Ala Arg Leu Arg Ile Val Lys Thr Leu Glu Asp
                85                  90                  95

Ile Asp Leu Gly Pro Thr Glu Lys Cys Val Arg Val Asn Ser Val Ser
            100                 105                 110

Ser Gly Leu Ala Glu Glu Asp Leu Glu Thr Leu Leu Gln Ser Arg Val
        115                 120                 125

Leu Pro Ser Ser Leu Met Leu Pro Lys Val Glu Ser Pro Glu Glu Ile
    130                 135                 140

Gln Trp Ala Val Cys Glu Glu Thr Leu Lys Val Gly Pro Gln Val Gly
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145 150 155 160

Leu Phe Leu Asp Ala Val Arg Phe Trp Arg Xaa Arg Leu Ser Ser His
165 170 175

Ile Gly Ala Xaa Ser Xaa Lys Glu Thr Leu Asp Xaa Leu Tyr Ala Arg
180 185 190

Gln Lys Ile Val Val Ile Ala Lys Ala Phe Gly Leu Gln Ala Val Xaa
195 200 205

Leu Xaa Xaa Ile Asp Phe Arg Asp Gly Xaa Xaa Leu Leu Arg Gln Ser
210 215 220

Arg Glu Gly Ala Ala Met Gly Phe Thr Gly Lys Gln Val Ile His Pro
225 230 235 240

Asn Gln Ile Ala Val Val Gln Glu Gln Phe Ser Pro Ser Pro Glu Lys
245 250 255

Ile Lys Trp Ala Glu Glu Leu Ile Ala Ala Phe Lys Glu His Gln Gln
260 265 270

Leu Gly Lys Gly Ala Phe Thr Phe Gln Gly Ser Met Ile Asp Met Pro
275 280 285

Leu Leu Lys Gln Ala Gln Asn Thr Val Thr Leu Ala Thr Ser Ile Lys
290 295 300

Glu Lys
305

<210> 535
<211> 64
<212> PRT
<213> Homo sapiens

<400> 535
Met Val Ser Pro Leu Ile Ser Ala Leu Phe His Val Pro Phe Leu Trp
1 5 10 15

Leu Gly Met Phe Phe Pro His Ser Leu Ser Gly Pro Phe Pro Ser His
20 25 30

Leu Arg Arg Ala Ser Ser Ser Arg Lys Pro Leu Val Lys Pro Pro Arg
35 40 45

Ala Arg Gln Tyr Pro Pro Leu Ala Ser Ser Gly Tyr Arg Gly Arg Ile
50 55 60

<210> 536
<211> 26
<212> PRT
<213> Homo sapiens

<400> 536
Met Ser Phe Pro His Ala Ser Thr Leu Pro Phe His Lys Leu Ser Asp
1   5   10   15

Leu Gln His Thr Leu Pro Asn His Gln Gly
            20   25

<210> 537
<211> 50
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (4)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (10)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (22)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (35)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (39)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (42)
<223> Xaa equals any amino acid

<400> 537
Val His Ala Xaa Thr Pro Phe Ala Gly Xaa Cys Phe Asp Pro Val Ser
1   5   10   15

Leu Tyr Trp Cys Tyr Xaa Asn Pro Gly Thr His Cys Tyr Pro Thr Leu
            20   25   30

Arg Gly Xaa Glu Gln Arg Xaa Pro Ser Xaa Arg Ser His Ile Val Leu
        35   40   45

Arg Ser
    50

<210> 538

<211> 57
<212> PRT
<213> Homo sapiens

<400> 538
Met Pro Pro His Arg Gln Thr Asp Gly Gln Met Gly Leu Pro Ala Pro
1 5 10 15

Ala Leu Trp Val Trp Gly Leu Leu Leu Ser Ser Ser Phe Gln Thr Leu
20 25 30

Leu Pro Ala Phe Pro Lys Pro Pro Ala Leu Asn Leu Gly Cys Ser Thr
35 40 45

Arg Pro Ile Pro Ser Phe Leu Lys Ile
50 55

<210> 539
<211> 93
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (24)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (65)
<223> Xaa equals any amino acid

<400> 539
Gln Val Ser Leu Pro Thr Arg Leu Leu Gln Met Pro Gly Met Gly Leu
1 5 10 15

Asp Ser Arg Phe Gln Ala Trp Xaa Pro Ser Pro Tyr Leu Gly Pro Gln
20 25 30

Pro Arg Ala Pro Arg Pro Gly Leu Gln Pro Gly Pro Ser Leu Arg Gly
35 40 45

Ala Glu Phe Arg Glu Ser Cys Pro Arg Ser Gln Lys Arg Gly Arg Glu
50 55 60

Xaa Gly Arg Pro Cys Pro Gly Cys Arg Pro Gly Gly Trp Gly Leu Pro
65 70 75 80

Ala Arg Leu Gly Gln Pro Gln Leu Gln Thr Gly Pro Gly
85 90

<210> 540
<211> 172
<212> PRT
<213> Homo sapiens

<220>

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<221> SITE
<222> (170)
<223> Xaa equals any amino acid

<400> 540
Met Arg Gly Ser Val Glu Cys Thr Trp Gly Trp Gly His Cys Ala Pro
 1               5                  10                  15

Ser Pro Leu Leu Leu Trp Thr Leu Leu Leu Phe Ala Ala Pro Phe Gly
            20                  25                  30

Leu Leu Gly Glu Lys Thr Arg Gln Leu Leu Glu Phe Asp Ser Thr Asn
        35                  40                  45

Val Ser Asp Thr Ala Ala Lys Pro Leu Gly Arg Pro Tyr Pro Pro Tyr
    50                  55                  60

Ser Leu Ala Asp Phe Ser Trp Asn Asn Ile Thr Asp Ser Leu Asp Pro
65                  70                  75                  80

Ala Thr Leu Ser Ala Thr Phe Gln Gly His Pro Met Asn Asp Pro Thr
                85                  90                  95

Arg Thr Phe Ala Asn Gly Ser Leu Ala Phe Arg Val Gln Ala Phe Ser
            100                 105                 110

Arg Ser Ser Arg Pro Ala Gln Pro Pro Arg Leu Leu His Thr Ala Asp
        115                 120                 125

Thr Cys Gln Leu Glu Val Ala Leu Ile Gly Ala Ser Pro Arg Gly Asn
    130                 135                 140

Arg Ser Leu Phe Gly Leu Glu Val Ala Thr Leu Gly Gln Gly Pro Asp
145                 150                 155                 160

Cys Pro Ser Met Gln Glu Gln His Ser Xaa Glu Arg
                165                 170


<210> 541
<211> 131
<212> PRT
<213> Homo sapiens

<400> 541
Met Arg Gly Ser Val Glu Cys Thr Trp Gly Trp Gly His Cys Ala Pro
 1               5                  10                  15

Ser Pro Leu Leu Leu Trp Thr Leu Leu Leu Phe Ala Ala Pro Phe Gly
            20                  25                  30

Leu Leu Gly Glu Lys Thr Arg Gln Leu Leu Glu Phe Asp Ser Thr Asn
        35                  40                  45

Val Ser Asp Thr Ala Ala Lys Pro Leu Gly Arg Pro Tyr Pro Pro Tyr
    50                  55                  60

Ser Leu Ala Asp Phe Ser Trp Asn Asn Ile Thr Asp Ser Leu Asp Pro
65                  70                  75                  80
```

Ala Thr Leu Ser Ala Thr Phe Gln Gly His Pro Met Asn Asp Pro Thr
85 90 95

Arg Thr Phe Ala Asn Gly Ser Leu Ala Phe Arg Ser Arg Pro Phe Pro
100 105 110

Gly Pro Ala Asp Gln Pro Asn Pro Leu Ala Ser Cys Thr Gln Gln Thr
115 120 125

Pro Val Ser
130

<210> 542
<211> 121
<212> PRT
<213> Homo sapiens

<400> 542
Met Cys Phe Leu Met Ile Phe Thr Phe Leu Val Cys Trp Met Pro Tyr
1 5 10 15

Ile Val Ile Cys Phe Leu Val Val Asn Gly His Gly His Leu Val Thr
20 25 30

Pro Thr Ile Ser Ile Val Ser Tyr Leu Phe Ala Lys Ser Asn Thr Val
35 40 45

Tyr Asn Pro Val Ile Tyr Val Phe Met Ile Arg Lys Phe Arg Arg Ser
50 55 60

Leu Leu Gln Leu Leu Cys Leu Arg Leu Leu Arg Cys Gln Arg Pro Ala
65 70 75 80

Lys Asp Leu Pro Ala Ala Gly Ser Glu Met Gln Ile Arg Pro Ile Val
85 90 95

Met Ser Gln Lys Asp Gly Asp Arg Pro Lys Lys Ser Asp Phe Gln Leu
100 105 110

Phe Phe His His Phe Tyr His His Gln
115 120

<210> 543

<211> 49
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (41)
<223> Xaa equals any amino acid

<400> 543
Met Gly Ala His Ser Phe Gly Phe Gln Leu Phe Met Ser Val Ser Val
1 5 10 15

Leu Trp Gly Arg Leu Cys Leu Tyr Gly Arg Phe Ser Val Ile Thr Phe
20 25 30

Ala Ser Pro Pro Thr Thr Phe Met Xaa Ile Gln Cys Cys Ser His Cys
35 40 45

Ser

<210> 544
<211> 484
<212> PRT
<213> Homo sapiens

<400> 544
Met Pro Arg His Leu Ser Gly Leu Leu Leu Leu Leu Trp Pro Leu Leu
1 5 10 15

Leu Leu Leu Pro Pro Thr Pro Ala Ala Pro Gly Pro Leu Ala Arg Pro
20 25 30

Gly Leu Arg Arg Leu Gly Thr Arg Gly Pro Gly Gly Ser Pro Gly Arg
35 40 45

Arg Pro Gly Ser Ala Val Pro Thr Arg Ala Pro Tyr Ser Gly Ala Gly
50 55 60

Gln Pro Gly Gly Ala Arg Gly Ala Gly Val Cys Arg Ser Arg Pro Leu
65 70 75 80

Asp Leu Val Phe Ile Ile Asp Ser Ser Arg Ser Val Arg Pro Leu Glu
85 90 95

Phe Thr Lys Val Lys Thr Phe Val Ser Gln Ile Ile Asp Thr Leu Asp
100 105 110

Ile Gly Ala Ala Asp Thr Arg Val Ala Val Val Asn Tyr Ala Ser Thr
115 120 125

Val Lys Ile Glu Phe His Leu Gln Thr His Ser Asp Lys Gln Ser Leu
130 135 140

Lys Gln Ala Val Ala Arg Ile Thr Pro Leu Ser Thr Gly Thr Met Ser
145 150 155 160

Gly Leu Ala Ile Gln Thr Ala Met Asp Glu Ala Phe Thr Val Glu Ala
165 170 175

Gly Ala Arg Gly Pro Thr Ser Asn Ile Pro Lys Val Ala Ile Ile Val
180 185 190

Thr Asp Gly Arg Pro Gln Asp Gln Val Asn Glu Val Ala Ala Arg Ala
195 200 205

Arg Ala Ser Gly Ile Glu Leu Tyr Ala Val Gly Val Asp Arg Ala Asp
210 215 220

Met Glu Ser Leu Lys Met Met Ala Ser Glu Pro Leu Asp Glu His Val
225 230 235 240

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Phe Tyr Val Glu Thr Tyr Gly Val Ile Glu Lys Leu Ser Ser Arg Phe
                245                 250                 255

Gln Glu Thr Phe Cys Ala Leu Asp Pro Cys Val Leu Gly Thr His Arg
            260                 265                 270

Cys Gln His Val Cys Val Ser Asp Gly Glu Gly Lys His His Cys Glu
        275                 280                 285

Cys Ser Gln Gly Tyr Ser Leu Asn Ala Asp Gln Lys Thr Cys Ser Ala
    290                 295                 300

Ile Asp Lys Cys Ala Leu Asn Thr His Gly Cys Glu His Ile Cys Val
305                 310                 315                 320

Asn Asp Arg Thr Gly Ser Tyr His Cys Glu Cys Tyr Glu Gly Tyr Thr
                325                 330                 335

Leu Asn Gln Asp Arg Lys Thr Cys Ser Ala Gln Asp Gln Cys Ala Phe
            340                 345                 350

Gly Thr His Gly Cys Gln His Ile Cys Val Asn Asp Arg Asp Gly Ser
        355                 360                 365

His His Cys Glu Cys Tyr Glu Gly Tyr Thr Leu Asn Ala Asp Asn Lys
    370                 375                 380

Thr Cys Ser Val Arg Ser Glu Cys Ala Gly Gly Ser His Gly Cys Gln
385                 390                 395                 400

His Leu Cys Val Asp Asp Gly Pro Ala Ala Tyr His Cys Asp Cys Phe
                405                 410                 415

Pro Gly Tyr Thr Leu Thr Glu Asp Arg Arg Thr Cys Ala Ala Ile Glu
            420                 425                 430

Glu Ala Arg Arg Leu Val Ser Thr Glu Asp Ala Cys Gly Cys Glu Ala
        435                 440                 445

Thr Leu Ala Phe Gln Glu Arg Ala Ser Ser Tyr Leu Gln Arg Leu Asn
    450                 455                 460

Ala Lys Leu Asp Asp Ile Leu Gly Lys Leu Gln Ala Asp Ala Tyr Gly
465                 470                 475                 480

Gln Ile His Arg


<210> 545
<211> 266
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (45)
<223> Xaa equals any amino acid
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<220>
<221> SITE
<222> (47)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (51)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (134)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (183)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (222)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (224)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (255)
<223> Xaa equals any amino acid

<400> 545
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Met Pro Arg His Leu Ser Gly Leu Leu Leu Leu Leu Trp Pro Leu Leu
  1               5                  10                  15

Leu Leu Leu Pro Pro Thr Pro Ala Ala Pro Gly Pro Leu Ala Arg Pro
             20                  25                  30

Gly Leu Arg Arg Leu Gly Thr Arg Gly Pro Gly Gly Xaa Pro Xaa Arg
         35                  40                  45

Arg Pro Xaa Ser Ala Val Pro Thr Arg Ala Pro Tyr Ser Gly Ala Gly
     50                  55                  60

Gln Pro Gly Gly Ala Arg Gly Ala Gly Val Cys Arg Ser Arg Pro Leu
 65                  70                  75                  80

Asp Leu Val Phe Ile Ile Asp Ser Ser Arg Ser Val Arg Pro Leu Glu
                 85                  90                  95

Phe Thr Lys Val Lys Thr Phe Val Ser Gln Ile Ile Asp Thr Leu Asp
            100                 105                 110

Ile Gly Ala Ala Asp Thr Arg Val Ala Val Val Asn Tyr Ala Ser Thr
        115                 120                 125

Val Lys Ile Glu Phe Xaa Leu Gln Thr His Ser Asp Lys Gln Ser Leu
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    130                 135                 140

Lys Gln Ala Val Ala Arg Ile Thr Pro Leu Ser Thr Gly Thr Met Ser
145                 150                 155                 160

Gly Leu Ala Ile Gln Thr Ala Met Asp Glu Ala Phe Thr Val Glu Ala
                165                 170                 175

Gly Ala Arg Gly Pro Thr Xaa Asn Ile Pro Lys Val Ala Ile Ile Val
            180                 185                 190

Thr Asp Gly Arg Pro Gln Asp Gln Val Asn Glu Val Ala Ala Arg Ala
        195                 200                 205

Arg Ala Ser Gly Ile Glu Leu Tyr Ala Val Gly Val Asp Xaa Ala Xaa
    210                 215                 220

Met Glu Ser Leu Gln Asp Glu Trp Pro Ala Lys Pro Leu Asp Glu His
225                 230                 235                 240

Val Phe Tyr Val Glu Thr Tyr Gly Val Ile Glu Lys Pro Ser Xaa Arg
                245                 250                 255

Phe Gln Glu Thr Leu Leu Arg Ser Trp Asn
            260                 265


<210> 546
<211> 5
<212> PRT
<213> Homo sapiens

<400> 546
Val Leu Leu Ile Leu
  1               5



<210> 547
<211> 84
<212> PRT
<213> Homo sapiens

<400> 547
Lys Met His Phe Asn Lys Asn Lys Ser Ile Leu Lys Ser Phe Ser Phe
  1               5                  10                  15

Val Arg Gly Asn Met Asn Glu Ile His Ser Tyr Leu Lys Thr Glu Tyr
             20                  25                  30

Phe Thr Ala Lys Thr Leu Asn Ile Ser Arg Ala Tyr His Ile Leu Asn
         35                  40                  45

Thr Leu Trp Ser Cys Ser Tyr Phe Asn Ile Pro Gly Ser Gly Gly Gln
     50                  55                  60

Leu Ala Cys Leu Trp Leu Arg Ile Cys Phe His Ala Cys Phe Leu Ser
 65                  70                  75                  80

Phe Phe Tyr Leu
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<210> 548
<211> 67
<212> PRT
<213> Homo sapiens

<400> 548
Met Ala Pro Ser Gly Pro Leu Leu Leu Val Leu Leu Val Pro Leu Ala
1   5   10   15

Ala Ala Arg Pro Gly Pro Thr Ser Val Pro Ala Gly Ala Ala Ala Cys
            20   25   30

Pro Cys Gly Gly Thr Ser Cys Arg Gly Trp Gly Ala Gly Pro Thr Pro
        35   40   45

Gly Arg Thr Ser Thr Cys Pro His Leu Thr Cys Pro Arg Ala Gly Thr
    50   55   60

Gly Ala Thr
65

<210> 549
<211> 14
<212> PRT
<213> Homo sapiens

<400> 549
Pro Gln Gly Pro Asn Asp Val Thr Ala Lys Leu Leu Cys Pro
1   5   10

<210> 550
<211> 6
<212> PRT
<213> Homo sapiens

<400> 550
Met Leu Leu Leu Tyr Leu
1   5

<210> 551
<211> 161
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (123)
<223> Xaa equals any amino acid

<220>
<221> SITE

<222> (129)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (145)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (146)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (157)
<223> Xaa equals any amino acid

<400> 551
Met Thr Thr Trp Ser Cys Leu Val Ala Met Ile Val Ser Gly Val Ile
1 5 10 15

Thr Ala Val Trp Ala Val Arg Ala Ala Pro Ile Trp Arg Ser Gln Val
20 25 30

Lys Gln Lys Met Arg Ile Gly Lys Gln Gly Asn Cys Arg Pro Pro Arg
35 40 45

Cys Ile Cys Ser Ala Leu Gly Leu Leu Ala Pro Trp Met Ala Val Val
50 55 60

Leu Ser Gln Leu Ser Val Arg Cys Val Val Ser Trp Val Gln Gly Lys
65 70 75 80

Pro Ser Ser Pro Arg Pro Arg Gly Ser Ala Ala Ser Pro Ala Pro Gly
85 90 95

Ala Thr Pro Pro Thr Pro Arg Lys Pro Val Ser Trp Leu Gly Tyr Arg
100 105 110

Glu Asn His Arg Pro Lys Lys Pro Lys Ser Xaa Thr Arg Cys Leu Val
115 120 125

Xaa Gln Asn Trp Ser Leu Pro Pro Ile Ser Lys Asp Arg Thr Ala Gly
130 135 140

Xaa Xaa Asp Thr Asn Arg Thr Arg Arg Ser Gly Leu Xaa Leu Arg Leu
145 150 155 160

Gly

<210> 552
<211> 325
<212> PRT
<213> Homo sapiens

<220>
<221> SITE

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<222> (10)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (136)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (186)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (234)
<223> Xaa equals any amino acid

<400> 552
Val Pro Pro Ala Val Cys Pro Ala Gly Xaa Phe Cys Gln Asn Gln Cys
  1               5                  10                  15

Phe Thr Lys Arg Gln Tyr Pro Glu Thr Lys Ile Ile Lys Thr Asp Gly
             20                  25                  30

Lys Gly Trp Gly Leu Val Ala Lys Arg Asp Ile Arg Lys Gly Glu Phe
         35                  40                  45

Val Asn Glu Tyr Val Gly Glu Leu Ile Asp Glu Glu Glu Cys Met Ala
     50                  55                  60

Arg Ile Lys His Ala His Glu Asn Asp Ile Thr His Phe Tyr Met Leu
 65                  70                  75                  80

Thr Ile Asp Lys Asp Arg Ile Ile Asp Ala Gly Pro Lys Gly Asn Tyr
                 85                  90                  95

Ser Arg Phe Met Asn His Ser Cys Gln Pro Asn Cys Glu Thr Leu Lys
            100                 105                 110

Trp Thr Val Asn Gly Asp Thr Arg Val Gly Leu Phe Ala Val Cys Asp
        115                 120                 125

Ile Pro Ala Gly Thr Glu Leu Xaa Phe Asn Tyr Asn Leu Asp Cys Leu
    130                 135                 140

Gly Asn Glu Lys Thr Val Cys Arg Cys Gly Ala Ser Asn Cys Ser Gly
145                 150                 155                 160

Phe Leu Gly Asp Arg Pro Lys Thr Ser Thr Thr Leu Ser Ser Glu Glu
                165                 170                 175

Lys Gly Lys Lys Thr Lys Lys Lys Thr Xaa Arg Arg Arg Ala Lys Gly
            180                 185                 190

Glu Gly Lys Arg Gln Ser Glu Asp Glu Cys Phe Arg Cys Gly Asp Gly
        195                 200                 205

Gly Gln Leu Val Leu Cys Asp Arg Lys Phe Cys Thr Lys Ala Tyr His
    210                 215                 220
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Leu Ser Cys Leu Gly Leu Gly Lys Arg Xaa Phe Gly Lys Trp Glu Cys
225 230 235 240

Pro Trp His His Cys Asp Val Cys Gly Lys Pro Ser Thr Ser Phe Cys
245 250 255

His Leu Cys Pro Asn Ser Phe Cys Lys Glu His Gln Asp Gly Thr Ala
260 265 270

Phe Ser Cys Thr Pro Asp Gly Arg Ser Tyr Cys Cys Glu His Asp Leu
275 280 285

Gly Ala Ala Ser Val Arg Ser Thr Lys Thr Glu Lys Pro Pro Pro Glu
290 295 300

Pro Gly Lys Pro Lys Gly Lys Arg Arg Arg Arg Arg Gly Trp Arg Arg
305 310 315 320

Val Thr Glu Gly Lys
325

<210> 553
<211> 40
<212> PRT
<213> Homo sapiens

<400> 553
Met Val Ala Met Val Phe Leu Lys Ile Ser Val Leu Pro Leu Met Cys
1 5 10 15

Arg Gly Gln Thr Lys His Lys Val Leu Arg Asp His Ala Tyr Pro Arg
20 25 30

Val Ser Gln Lys Arg Gly His Ile
35 40

<210> 554
<211> 173
<212> PRT
<213> Homo sapiens.

<400> 554
Met Val Phe Leu Lys Phe Phe Cys Met Ser Phe Phe Cys His Leu Cys
1 5 10 15

Gln Gly Tyr Phe Asp Gly Pro Leu Tyr Pro Glu Met Ser Asn Gly Thr
20 25 30

Leu His His Tyr Phe Val Pro Asp Gly Asp Tyr Glu Glu Asn Asp Asp
35 40 45

Pro Glu Lys Cys Gln Leu Leu Phe Arg Val Ser Asp His Arg Arg Cys
50 55 60

Ser Gln Gly Glu Gly Ser Gln Val Gly Ser Leu Leu Ser Leu Thr Leu
65 70 75 80

Arg Glu Glu Phe Thr Val Leu Gly His Gln Val Glu Gly Cys Trp Ala
85 90 95

Arg Ala Gly Gly His Gln Gln Lys His Leu Leu Arg Pro Arg Arg Gly
100 105 110

Arg Glu Leu Trp Gln Val Pro Ala Ala Gly Val Pro Pro Asp Arg Gly
115 120 125

Met Pro Thr Pro Thr Arg Thr Asn Pro Ser Leu Ser Trp Arg Ala Ser
130 135 140

Ser Ser Arg Ala Arg Asn Arg Thr Ala Gly Arg Arg Ala Gly Ser Thr
145 150 155 160

Arg Thr Phe Trp Glu Cys Trp Ser Thr Pro Gly Pro Cys
165 170

<210> 555
<211> 48
<212> PRT
<213> Homo sapiens

<400> 555
Met Met Leu Tyr Gln Asn Met Leu Leu Tyr Phe Arg Ile Ile Gly Val
1 5 10 15

Leu Ala Leu Asn Phe Ser Ile Ser Pro Ile Phe Phe His Gly Ser Leu
20 25 30

Gly Lys Leu Tyr Val Tyr Ser Ala Ala Lys Tyr Ser Leu Glu Leu Lys
35 40 45

<210> 556
<211> 10
<212> PRT
<213> Homo sapiens

<400> 556
Ile Tyr Gln His Phe Ser Leu Trp Leu Gly
1 5 10

<210> 557
<211> 4
<212> PRT
<213> Homo sapiens

<400> 557
Met Phe Lys Met
1

<210> 558
<211> 201
<212> PRT
<213> Homo sapiens

<400> 558
Met Lys Leu Leu Ile Leu Phe Leu Ser His Leu Leu Ser Leu Ala Phe
1 5 10 15

Gly Ile Leu Cys Leu Ser Val Thr Val Ile Leu Ser Leu Leu Leu Ser
20 25 30

Phe Ser Lys Arg Gly Phe Ser Val Arg Ser Phe Gly Thr Gly Thr His
35 40 45

Val Lys Leu Pro Gly Pro Ala Pro Asp Lys Pro Asn Val Tyr Asp Phe
50 55 60

Lys Thr Thr Tyr Asp Gln Met Tyr Asn Asp Leu Leu Arg Lys Asp Lys
65 70 75 80

Glu Leu Tyr Thr Gln Asn Gly Ile Leu His Met Leu Asp Arg Asn Lys
85 90 95

Arg Ile Lys Pro Arg Pro Glu Arg Phe Gln Asn Cys Lys Asp Leu Phe
100 105 110

Asp Leu Ile Leu Thr Cys Glu Glu Arg Val Tyr Asp Gln Val Val Glu
115 120 125

Asp Leu Asn Ser Arg Glu Gln Glu Thr Cys Gln Pro Val His Val Val
130 135 140

Asn Val Asp Ile Gln Asp Asn His Glu Glu Ala Thr Leu Gly Ala Phe
145 150 155 160

Leu Ile Cys Glu Leu Cys Gln Cys Ile Gln His Thr Glu Asp Met Glu
165 170 175

Asn Glu Ile Asp Glu Leu Leu Gln Glu Phe Glu Glu Lys Ser Gly Arg
180 185 190

Thr Phe Leu His Thr Val Cys Phe Tyr
195 200

<210> 559
<211> 392
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (251)
<223> Xaa equals any amino acid

<400> 559
Met Ala Pro Trp Pro Pro Lys Gly Leu Val Pro Ala Val Leu Trp Gly
1 5 10 15

Leu Ser Leu Phe Leu Asn Leu Pro Gly Pro Ile Trp Leu Gln Pro Ser
20 25 30

Pro Pro Pro Gln Ser Ser Pro Pro Pro Gln Pro His Pro Cys His Thr
35 40 45

Cys Arg Gly Leu Val Asp Ser Phe Asn Lys Gly Leu Glu Arg Thr Ile
50 55 60

Arg Asp Asn Phe Gly Gly Gly Asn Thr Ala Trp Glu Glu Glu Asn Leu
65 70 75 80

Ser Lys Tyr Lys Asp Ser Glu Thr Arg Leu Val Glu Val Leu Glu Gly
85 90 95

Val Cys Ser Lys Ser Asp Phe Glu Cys His Arg Leu Leu Glu Leu Ser
100 105 110

Glu Glu Leu Val Glu Ser Trp Trp Phe His Lys Gln Gln Glu Ala Pro
115 120 125

Asp Leu Phe Gln Trp Leu Cys Ser Asp Ser Leu Lys Leu Cys Cys Pro
130 135 140

Ala Gly Thr Phe Gly Pro Ser Cys Leu Pro Cys Pro Gly Gly Thr Glu
145 150 155 160

Arg Pro Cys Gly Gly Tyr Gly Gln Cys Glu Gly Glu Gly Thr Arg Gly
165 170 175

Gly Ser Gly His Cys Asp Cys Gln Ala Gly Tyr Gly Gly Glu Ala Cys
180 185 190

Gly Gln Cys Gly Leu Gly Tyr Phe Glu Ala Glu Arg Asn Ala Ser His
195 200 205

Leu Val Cys Ser Ala Cys Phe Gly Pro Cys Ala Arg Cys Ser Gly Pro
210 215 220

Glu Glu Ser Asn Cys Leu Gln Cys Lys Lys Gly Trp Ala Leu His His
225 230 235 240

Leu Lys Cys Val Asp Cys Ala Lys Ala Cys Xaa Gly Cys Met Gly Ala
245 250 255

Gly Pro Gly Arg Cys Lys Lys Cys Ser Pro Gly Tyr Gln Gln Val Gly
260 265 270

Ser Lys Cys Leu Asp Val Asp Glu Cys Glu Thr Glu Val Cys Pro Gly
275 280 285

Glu Asn Lys Gln Cys Glu Asn Thr Glu Gly Gly Tyr Arg Cys Ile Cys
290 295 300

Ala Glu Gly Tyr Lys Gln Met Glu Gly Ile Cys Val Lys Glu Gln Ile
305 310 315 320

Pro Glu Ser Ala Gly Phe Phe Ser Glu Met Thr Glu Asp Glu Leu Val
325 330 335

Val Leu Gln Gln Met Phe Phe Gly Ile Ile Ile Cys Ala Leu Ala Thr
            340   345   350

Leu Ala Ala Lys Gly Asp Leu Val Phe Thr Ala Ile Phe Ile Gly Ala
        355   360   365

Val Ala Ala Met Thr Gly Tyr Trp Leu Ser Glu Arg Ser Asp Arg Val
    370   375   380

Leu Glu Gly Phe Ile Lys Gly Arg
385   390

<210> 560
<211> 63
<212> PRT
<213> Homo sapiens

<400> 560
Met Thr Glu Asp Glu Leu Val Val Leu Gln Gln Met Phe Phe Gly Ile
1   5   10   15

Ile Ile Cys Ala Leu Ala Thr Leu Ala Ala Lys Gly Asp Leu Val Phe
            20   25   30

Thr Ala Ile Phe Ile Gly Ala Val Ala Ala Met Thr Gly Tyr Trp Leu
        35   40   45

Ser Glu Arg Ser Asp Arg Val Leu Glu Gly Phe Ile Lys Gly Arg
    50   55   60

<210> 561
<211> 102
<212> PRT
<213> Homo sapiens

<400> 561
Met Thr Val Arg Arg Leu Ser Leu Leu Cys Arg Asp Leu Trp Ala Leu
1   5   10   15

Trp Leu Leu Leu Lys Ala Gly Ala Val Arg Gly Ala Arg Ala Gly Pro
            20   25   30

Arg Leu Pro Gly Arg Cys Cys Gly Ala Thr Cys Gly Asp Ala Gly Arg
        35   40   45

Gly Trp Thr Phe Trp Ala Gln Pro Cys Pro Gln Lys Leu Leu Gly Gln
    50   55   60

Lys Pro Gly Ala Gly Gly Cys Arg Gly Trp Val Leu Gly Trp Val Pro
65   70   75   80

Pro Arg Pro Glu Glu Pro Cys Ser Leu Ala Gly Lys Val Cys Thr Gly
                85   90   95

Leu Ala Arg Trp Met Val
            100

<210> 562
<211> 53
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (41)
<223> Xaa equals any amino acid

<400> 562
Met Cys Lys Ala Val Cys Lys His Arg Leu Arg Leu Phe Ala Val Ser
1 5 10 15

Ser Phe Ser Leu Gly Leu Gly Trp Val Cys Val Leu Val Leu Met Leu
20 25 30

Trp Pro Val Arg Leu Ser Leu Ala Xaa Arg Pro Val Gln Leu Gln Gln
35 40 45

Arg Arg Ser His Cys
50

<210> 563
<211> 472
<212> PRT
<213> Homo sapiens

<400> 563
Met Lys Phe Leu Ile Phe Ala Phe Phe Gly Gly Val His Leu Leu Ser
1 5 10 15

Leu Cys Ser Gly Lys Ala Ile Cys Lys Asn Gly Ile Ser Lys Arg Thr
20 25 30

Phe Glu Glu Ile Lys Glu Glu Ile Ala Ser Cys Gly Asp Val Ala Lys
35 40 45

Ala Ile Ile Asn Leu Ala Val Tyr Gly Lys Ala Gln Asn Arg Ser Tyr
50 55 60

Glu Arg Leu Ala Leu Leu Val Asp Thr Val Gly Pro Arg Leu Ser Gly
65 70 75 80

Ser Lys Asn Leu Glu Lys Ala Ile Gln Ile Met Tyr Gln Asn Leu Gln
85 90 95

Gln Asp Gly Leu Glu Lys Val His Leu Glu Pro Val Arg Ile Pro His
100 105 110

Trp Glu Arg Gly Glu Glu Ser Ala Val Met Leu Glu Pro Arg Ile His
115 120 125

Lys Ile Ala Ile Leu Gly Leu Gly Ser Ser Ile Gly Thr Pro Pro Glu
130 135 140

Gly Ile Thr Ala Glu Val Leu Val Val Thr Ser Phe Asp Glu Leu Gln

145 150 155 160

Arg Arg Ala Ser Glu Ala Arg Gly Lys Ile Val Val Tyr Asn Gln Pro
165 170 175

Tyr Ile Asn Tyr Ser Arg Thr Val Gln Tyr Arg Thr Gln Gly Ala Val
180 185 190

Glu Ala Ala Lys Val Gly Ala Leu Ala Ser Leu Ile Arg Ser Val Ala
195 200 205

Ser Phe Ser Ile Tyr Ser Pro His Thr Gly Ile Gln Glu Tyr Gln Asp
210 215 220

Gly Val Pro Lys Ile Pro Thr Ala Cys Ile Thr Val Glu Asp Ala Glu
225 230 235 240

Met Met Ser Arg Met Ala Ser His Gly Ile Lys Ile Val Ile Gln Leu
245 250 255

Lys Met Gly Ala Lys Thr Tyr Pro Asp Thr Asp Ser Phe Asn Thr Val
260 265 270

Ala Glu Ile Thr Gly Ser Lys Tyr Pro Glu Gln Val Val Leu Val Ser
275 280 285

Gly His Leu Asp Ser Trp Asp Val Gly Gln Gly Ala Met Asp Asp Gly
290 295 300

Gly Gly Ala Phe Ile Ser Trp Glu Ala Leu Ser Leu Ile Lys Asp Leu
305 310 315 320

Gly Leu Arg Pro Lys Arg Thr Leu Arg Leu Val Leu Trp Thr Ala Glu
325 330 335

Glu Gln Gly Gly Val Gly Ala Phe Gln Tyr Tyr Gln Leu His Lys Val
340 345 350

Asn Ile Ser Asn Tyr Ser Leu Val Met Glu Ser Asp Ala Gly Thr Phe
355 360 365

Leu Pro Thr Gly Leu Gln Phe Thr Gly Ser Glu Lys Ala Arg Ala Ile
370 375 380

Met Glu Glu Val Met Ser Leu Leu Gln Pro Leu Asn Ile Thr Gln Val
385 390 395 400

Leu Ser His Gly Glu Gly Thr Asp Ile Asn Phe Trp Ile Gln Ala Gly
405 410 415

Val Pro Gly Ala Ser Leu Leu Asp Asp Leu Tyr Lys Tyr Phe Phe Phe
420 425 430

His His Ser His Gly Asp Thr Met Thr Val Met Asp Pro Lys Gln Met
435 440 445

Asn Val Ala Ala Ala Val Trp Ala Val Val Ser Tyr Val Val Ala Asp
450 455 460

Met Glu Glu Met Leu Pro Arg Ser
465 470

<210> 564
<211> 178
<212> PRT
<213> Homo sapiens

<400> 564
Ser Ile Tyr Ser Pro His Thr Gly Ile Gln Glu Tyr Gln Asp Gly Val
1 5 10 15

Pro Lys Ile Pro Thr Ala Cys Ile Thr Val Glu Asp Ala Glu Met Met
20 25 30

Ser Arg Met Ala Ser His Gly Ile Lys Ile Val Ile Gln Leu Lys Met
35 40 45

Gly Ala Lys Thr Tyr Pro Asp Thr Asp Ser Phe Asn Thr Val Ala Glu
50 55 60

Ile Thr Gly Ser Lys Tyr Pro Glu Gln Val Val Leu Val Ser Gly His
65 70 75 80

Leu Asp Ser Trp Asp Val Gly Gln Gly Ala Met Asp Asp Gly Gly Gly
85 90 95

Ala Phe Ile Ser Trp Glu Ala Leu Ser Leu Ile Lys Asp Leu Gly Leu
100 105 110

Arg Pro Lys Arg Thr Leu Arg Leu Val Leu Trp Thr Ala Glu Glu Gln
115 120 125

Gly Gly Val Gly Ala Phe Gln Tyr Tyr Gln Leu His Lys Val Asn Ile
130 135 140

Ser Asn Tyr Ser Leu Val Met Glu Ser Asp Ala Gly Thr Phe Leu Pro
145 150 155 160

Thr Gly Leu Gln Phe Thr Gly Ser Glu Lys Ala Arg Ala Ser Trp Arg
165 170 175

Arg Leu

<210> 565
<211> 199
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (142)
<223> Xaa equals any amino acid

<400> 565
Met Lys Leu Gly Cys Val Leu Met Ala Trp Ala Leu Tyr Leu Ser Leu
1 5 10 15

Gly Val Leu Trp Val Ala Gln Met Leu Leu Ala Ala Ser Phe Glu Thr
20 25 30

Leu Gln Cys Glu Gly Pro Val Cys Thr Glu Glu Ser Ser Cys His Thr
35 40 45

Glu Asp Asp Leu Thr Asp Ala Arg Glu Ala Gly Phe Gln Val Lys Ala
50 55 60

Tyr Thr Phe Ser Glu Pro Phe His Leu Ile Val Ser Tyr Asp Trp Leu
65 70 75 80

Ile Leu Gln Gly Pro Ala Lys Pro Val Phe Glu Gly Asp Leu Leu Val
85 90 95

Leu Arg Cys Gln Ala Trp Gln Asp Trp Pro Leu Thr Gln Val Thr Phe
100 105 110

Tyr Arg Asp Gly Ser Ala Leu Gly Pro Pro Gly Pro Asn Arg Glu Phe
115 120 125

Ser Ile Thr Val Val Gln Lys Ala Asp Ser Gly His Tyr Xaa Cys Ser
130 135 140

Gly Ile Phe Gln Ser Pro Gly Pro Gly Ile Pro Glu Thr Ala Ser Val
145 150 155 160

Val Ala Ile Thr Val Gln Glu Leu Phe Pro Ala Pro Ile Leu Leu Leu
165 170 175

Gln Gly Trp Lys Asp Ser Ala Lys Gln Gly Gly Ser Pro Gln Asn Ser
180 185 190

Arg Ser Pro Gln Leu Gln Lys
195

<210> 566
<211> 2
<212> PRT
<213> Homo sapiens

<400> 566
Ser Trp
1

<210> 567
<211> 32
<212> PRT
<213> Homo sapiens

<400> 567
Cys Leu Glu Thr Phe Trp Ser Leu Tyr Leu Gly Gly Trp Gly Met Val
1 5 10 15

Gly Cys Val Cys Tyr Trp His Pro Val Asn Arg Ser Gln Gly Cys Arg
20 25 30

<210> 568
<211> 283
<212> PRT
<213> Homo sapiens

<400> 568
Met Tyr Leu Ser Ala Leu Gln Ser Leu Ile Pro Ser Leu Phe Ala Leu
1   5   10   15

Val Leu Gln Asn Ala Pro Phe Ser Ser Lys Ala Lys Leu His Gly Glu
            20   25   30

Val Pro Gln Ile Glu Val Thr Arg Phe Pro Arg Pro Met Ser Pro Leu
        35   40   45

Gln Asp Val Ser Thr Ile Ile Gly Ser Arg Glu Gln Leu Ala Val Leu
    50   55   60

Leu Gln Leu Tyr Asp Tyr Gln Leu Glu Gln Glu Gly Thr Thr Gly Trp
65   70   75   80

Glu Ser Leu Leu Trp Val Val Asn Gln Leu Leu Pro Gln Leu Ile Glu
                85   90   95

Ile Val Gly Lys Ile Asn Val Thr Ser Thr Ala Cys Val His Glu Phe
            100   105   110

Ser Arg Phe Phe Trp Arg Leu Cys Arg Thr Phe Gly Lys Ile Phe Thr
        115   120   125

Asn Thr Lys Val Lys Pro Gln Phe Gln Glu Ile Leu Arg Leu Ser Glu
    130   135   140

Glu Asn Ile Asp Ser Ser Ala Gly Asn Gly Val Leu Thr Lys Ala Thr
145   150   155   160

Val Pro Ile Tyr Ala Thr Gly Val Leu Thr Cys Tyr Ile Gln Glu Glu
                165   170   175

Asp Arg Lys Leu Leu Val Gly Phe Leu Glu Asp Val Met Thr Leu Leu
            180   185   190

Ser Leu Ser His Ala Pro Leu Asp Ser Leu Lys Ala Ser Phe Val Glu
        195   200   205

Leu Gly Ala Asn Pro Ala Tyr His Glu Leu Leu Leu Thr Val Leu Trp
    210   215   220

Tyr Gly Val Val His Thr Ser Ala Leu Val Arg Cys Thr Ala Ala Arg
225   230   235   240

Met Phe Glu Val Cys Gln His Met Pro Leu Leu Val Ser Ile Ile Met
                245   250   255

Ile Phe Phe Phe Leu Arg Arg Arg Arg Glu Phe Phe Leu Ile Lys Arg
            260   265   270

Leu Cys Ile Ser Lys Lys Lys Lys Lys Lys Lys
275 280

<210> 569
<211> 286
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (204)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (224)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (228)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (264)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (271)
<223> Xaa equals any amino acid

<400> 569
Met Tyr Leu Ser Ala Leu Gln Ser Leu Ile Pro Ser Leu Phe Ala Leu
1 5 10 15

Val Leu Gln Asn Ala Pro Phe Ser Ser Lys Ala Lys Leu His Gly Glu
20 25 30

Val Pro Gln Ile Glu Val Thr Arg Phe Pro Arg Pro Met Ser Pro Leu
35 40 45

Gln Asp Val Ser Thr Ile Ile Gly Ser Arg Glu Gln Leu Ala Val Leu
50 55 60

Leu Gln Leu Tyr Asp Tyr Gln Leu Glu Gln Glu Gly Thr Thr Gly Trp
65 70 75 80

Glu Ser Leu Leu Trp Val Val Asn Gln Leu Leu Pro Gln Leu Ile Glu
85 90 95

Ile Val Gly Lys Ile Asn Val Thr Ser Thr Ala Cys Val His Glu Phe
100 105 110

Ser Arg Phe Phe Trp Arg Leu Cys Arg Thr Phe Gly Lys Ile Phe Thr
115 120 125

Asn Thr Lys Val Lys Pro Gln Phe Gln Glu Ile Leu Arg Leu Ser Glu
130 135 140

Glu Asn Ile Asp Ser Ser Ala Gly Asn Gly Val Leu Thr Lys Ala Thr
145 150 155 160

Val Pro Ile Tyr Ala Thr Gly Val Leu Thr Cys Tyr Ile Gln Glu Glu
165 170 175

Asp Arg Lys Leu Leu Val Gly Phe Leu Glu Asp Val Met Thr Leu Leu
180 185 190

Ser Leu Ser His Ala Pro Leu Asp Ser Leu Lys Xaa Ser Phe Val Glu
195 200 205

Leu Gly Ala Asn Gln Ala Tyr His Glu Leu Leu Leu Thr Val Leu Xaa
210 215 220

Tyr Gly Val Xaa His Thr Ser Ala Leu Val Arg Cys Thr Ala Ala Arg
225 230 235 240

Met Phe Glu Leu Leu Val Lys Gly Val Asn Glu Thr Leu Val Ala Gln
245 250 255

Arg Val Val Pro Ala Leu His Xaa Leu Ser Pro Val Asp Pro Xaa Asn
260 265 270

Leu Cys Gln Asp Cys His Asn Phe Gln Pro Leu Gly Leu Phe
275 280 285

<210> 570
<211> 45
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (43)
<223> Xaa equals any amino acid

<400> 570
Met Gln Ala Pro Leu Gln Asp Cys Gly Arg Ser Val Ser Leu Arg Leu
1 5 10 15

Ala Cys Val Leu Ala Pro Leu Thr Thr Ser Ser Arg Gly Cys His Leu
20 25 30

Gln Leu Pro Gln Asp Lys Gly Lys Ala Arg Xaa Asp Ser
35 40 45

<210> 571
<211> 305
<212> PRT
<213> Homo sapiens

<400> 571
Met Gly Ile Leu Leu Gly Leu Leu Leu Leu Gly His Leu Thr Val Asp

```
1               5                   10                  15
Thr Tyr Gly Arg Pro Ile Leu Glu Val Pro Glu Ser Val Thr Gly Pro
            20                  25                  30
Trp Lys Gly Asp Val Asn Leu Pro Cys Thr Tyr Asp Pro Leu Gln Gly
        35                  40                  45
Tyr Thr Gln Val Leu Val Lys Trp Leu Val Gln Arg Gly Ser Asp Pro
    50                  55                  60
Val Thr Ile Phe Leu Arg Asp Ser Ser Gly Asp His Ile Gln Gln Ala
65                  70                  75                  80
Lys Tyr Gln Gly Arg Leu His Val Ser His Lys Val Pro Gly Asp Val
                85                  90                  95
Ser Leu Gln Leu Ser Thr Leu Glu Met Asp Asp Arg Ser His Tyr Thr
            100                 105                 110
Cys Glu Val Thr Trp Gln Thr Pro Asp Gly Asn Gln Val Val Arg Asp
        115                 120                 125
Lys Ile Thr Glu Leu Arg Val Gln Lys His Ser Ser Lys Leu Leu Lys
    130                 135                 140
Thr Lys Thr Glu Ala Pro Thr Thr Met Thr Tyr Pro Leu Lys Ala Thr
145                 150                 155                 160
Ser Thr Val Lys Gln Ser Trp Asp Trp Thr Thr Asp Met Asp Gly Tyr
                165                 170                 175
Leu Gly Glu Thr Ser Ala Gly Pro Gly Lys Ser Leu Pro Val Phe Ala
            180                 185                 190
Ile Ile Leu Ile Ile Ser Leu Cys Cys Met Val Val Phe Thr Met Ala
        195                 200                 205
Tyr Ile Met Leu Cys Arg Lys Thr Ser Gln Gln Glu His Val Tyr Glu
    210                 215                 220
Ala Ala Arg Ala His Ala Arg Glu Ala Asn Asp Ser Gly Glu Thr Met
225                 230                 235                 240
Arg Val Ala Ile Phe Ala Ser Gly Cys Ser Ser Asp Glu Pro Thr Ser
                245                 250                 255
Gln Asn Leu Gly Asn Asn Tyr Ser Asp Glu Pro Cys Ile Gly Gln Glu
            260                 265                 270
Tyr Gln Ile Ile Ala Gln Ile Asn Gly Asn Tyr Ala Arg Leu Leu Asp
        275                 280                 285
Thr Val Pro Leu Asp Tyr Glu Phe Leu Ala Thr Glu Gly Lys Ser Val
    290                 295                 300
Cys
305
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<210> 572
<211> 72
<212> PRT
<213> Homo sapiens

<400> 572
Met Lys Phe Val Pro Cys Leu Leu Leu Val Thr Leu Ser Cys Leu Gly
1 5 10 15

Thr Leu Gly Gln Ala Pro Arg Gln Lys Gln Gly Ser Thr Gly Glu Glu
20 25 30

Phe His Phe Gln Thr Gly Gly Arg Asp Ser Cys Thr Met Arg Pro Ser
35 40 45

Ser Leu Gly Gln Gly Ala Gly Glu Val Trp Leu Arg Val Arg Leu Pro
50 55 60

Gln His Arg Pro Asp Leu Leu Val
65 70

<210> 573
<211> 121
<212> PRT
<213> Homo sapiens

<400> 573
Met Gly Leu Trp Leu Gly Met Leu Ala Cys Val Phe Leu Ala Thr Ala
1 5 10 15

Ala Phe Val Ala Tyr Thr Ala Arg Leu Asp Trp Lys Leu Ala Ala Glu
20 25 30

Glu Ala Lys Lys His Ser Gly Arg Gln Gln Gln Gln Arg Ala Glu Ser
35 40 45

Thr Ala Thr Arg Pro Gly Pro Glu Lys Ala Val Leu Ser Ser Val Ala
50 55 60

Thr Gly Ser Ser Pro Gly Ile Thr Leu Thr Thr Tyr Ser Arg Ser Glu
65 70 75 80

Cys His Val Asp Phe Phe Arg Thr Pro Glu Glu Ala His Ala Leu Ser
85 90 95

Ala Pro Thr Ser Arg Leu Ser Val Lys Gln Leu Val Ile Arg Arg Gly
100 105 110

Ala Ala Leu Gly Ala Ala Ser Ala His
115 120

<210> 574
<211> 509
<212> PRT
<213> Homo sapiens

<400> 574

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Met Thr Trp Arg Met Gly Pro Arg Phe Thr Met Leu Leu Ala Met Trp
  1               5                  10                  15

Leu Val Cys Gly Ser Glu Pro His Pro His Ala Thr Ile Arg Gly Ser
             20                  25                  30

His Gly Gly Arg Lys Val Pro Leu Val Ser Pro Asp Ser Ser Arg Pro
         35                  40                  45

Ala Arg Phe Leu Arg His Thr Gly Arg Ser Arg Gly Ile Glu Arg Ser
     50                  55                  60

Thr Leu Glu Glu Pro Asn Leu Gln Pro Leu Gln Arg Arg Arg Ser Val
 65                  70                  75                  80

Pro Val Leu Arg Leu Ala Arg Pro Thr Glu Pro Pro Ala Arg Ser Asp
                 85                  90                  95

Ile Asn Gly Ala Ala Val Arg Pro Glu Gln Arg Pro Ala Ala Arg Gly
            100                 105                 110

Ser Pro Arg Glu Met Ile Arg Asp Glu Gly Ser Ser Ala Arg Ser Arg
        115                 120                 125

Met Leu Arg Phe Pro Ser Gly Ser Ser Ser Pro Asn Ile Leu Ala Ser
    130                 135                 140

Phe Ala Gly Lys Asn Arg Val Trp Val Ile Ser Ala Pro His Ala Ser
145                 150                 155                 160

Glu Gly Tyr Tyr Arg Leu Met Met Ser Leu Leu Lys Asp Asp Val Tyr
                165                 170                 175

Cys Glu Leu Ala Glu Arg His Ile Gln Gln Ile Val Leu Phe His Gln
            180                 185                 190

Ala Gly Glu Glu Gly Gly Lys Val Arg Arg Ile Thr Ser Glu Gly Gln
        195                 200                 205

Ile Leu Glu Gln Pro Leu Asp Pro Ser Leu Ile Pro Lys Leu Met Ser
    210                 215                 220

Phe Leu Lys Leu Glu Lys Gly Lys Phe Gly Met Val Leu Leu Lys Lys
225                 230                 235                 240

Thr Leu Gln Val Glu Glu Arg Tyr Pro Tyr Pro Val Arg Leu Glu Ala
                245                 250                 255

Met Tyr Glu Val Ile Asp Gln Gly Pro Ile Arg Arg Ile Glu Lys Ile
            260                 265                 270

Arg Gln Lys Gly Phe Val Gln Lys Cys Lys Ala Ser Gly Val Glu Gly
        275                 280                 285

Gln Val Val Ala Glu Gly Asn Asp Gly Gly Gly Gly Ala Gly Arg Pro
    290                 295                 300

Ser Leu Gly Ser Glu Lys Lys Lys Glu Asp Pro Arg Arg Ala Gln Val
305                 310                 315                 320

Pro Pro Thr Arg Glu Ser Arg Val Lys Val Leu Arg Lys Leu Ala Ala
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325 330 335

Thr Ala Pro Ala Phe Pro Gln Pro Pro Ser Thr Pro Arg Ala Thr Thr
340 345 350

Leu Pro Pro Ala Pro Ala Thr Thr Val Thr Arg Ser Thr Ser Arg Ala
355 360 365

Val Thr Val Ala Ala Arg Pro Met Thr Thr Thr Ala Phe Pro Thr Thr
370 375 380

Gln Arg Pro Trp Thr Pro Ser Pro Ser His Arg Pro Pro Thr Thr Thr
385 390 395 400

Glu Val Ile Thr Ala Arg Arg Pro Ser Val Ser Glu Asn Leu Tyr Pro
405 410 415

Pro Ser Arg Lys Asp Gln His Arg Glu Arg Pro Gln Thr Thr Arg Arg
420 425 430

Pro Ser Lys Ala Thr Ser Leu Glu Ser Phe Thr Asn Ala Pro Pro Thr
435 440 445

Thr Ile Ser Glu Pro Ser Thr Arg Ala Ala Gly Pro Gly Arg Phe Arg
450 455 460

Asp Asn Arg Met Asp Arg Arg Glu His Gly His Arg Asp Pro Asn Val
465 470 475 480

Val Pro Gly Pro Pro Lys Pro Ala Lys Glu Lys Pro Pro Lys Lys Lys
485 490 495

Ala Gln Asp Lys Ile Leu Ser Asn Glu Tyr Glu Glu Val
500 505

<210> 575
<211> 554
<212> PRT
<213> Homo sapiens

<400> 575
Met Gly Pro Arg Phe Thr Met Leu Leu Ala Met Trp Leu Val Cys Gly
1 5 10 15

Ser Glu Pro His Pro His Ala Thr Ile Arg Gly Ser His Gly Gly Arg
20 25 30

Lys Val Pro Leu Val Ser Pro Asp Ser Ser Arg Pro Ala Arg Phe Leu
35 40 45

Arg His Thr Gly Arg Ser Arg Gly Ile Glu Arg Ser Thr Leu Glu Glu
50 55 60

Pro Asn Leu Gln Pro Leu Gln Arg Arg Arg Ser Val Pro Val Leu Arg
65 70 75 80

Leu Ala Arg Pro Thr Glu Pro Pro Ala Arg Ser Asp Ile Asn Gly Ala
85 90 95

Ala Val Arg Pro Glu Gln Arg Pro Ala Ala Arg Gly Ser Pro Arg Glu
100 105 110

Met Ile Arg Asp Glu Gly Ser Ser Ala Arg Ser Arg Met Leu Arg Phe
115 120 125

Pro Ser Gly Ser Ser Ser Pro Asn Ile Leu Ala Ser Phe Ala Gly Lys
130 135 140

Asn Arg Val Trp Val Ile Ser Ala Pro His Ala Ser Glu Gly Tyr Tyr
145 150 155 160

Arg Leu Met Met Ser Leu Leu Lys Asp Asp Val Tyr Cys Glu Leu Ala
165 170 175

Glu Arg His Ile Gln Gln Ile Val Leu Phe His Gln Ala Gly Glu Glu
180 185 190

Gly Gly Lys Val Arg Arg Ile Thr Ser Glu Gly Gln Ile Leu Glu Gln
195 200 205

Pro Leu Asp Pro Ser Leu Ile Pro Lys Leu Met Ser Phe Leu Lys Leu
210 215 220

Glu Lys Gly Lys Phe Gly Met Val Leu Leu Lys Lys Thr Leu Gln Val
225 230 235 240

Glu Glu Arg Tyr Pro Tyr Pro Val Arg Leu Glu Ala Met Tyr Glu Val
245 250 255

Ile Asp Gln Gly Pro Ile Arg Arg Ile Glu Lys Ile Arg Gln Lys Gly
260 265 270

Phe Val Gln Lys Cys Lys Ala Ser Gly Val Glu Gly Gln Val Val Ala
275 280 285

Glu Gly Asn Asp Gly Gly Gly Gly Ala Gly Arg Pro Ser Gln Gly Ser
290 295 300

Glu Lys Lys Lys Glu Asp Pro Arg Arg Ala Gln Val Pro Pro Thr Arg
305 310 315 320

Glu Ser Arg Val Lys Val Leu Arg Lys Leu Ala Ala Thr Ala Pro Ala
325 330 335

Phe Pro Gln Pro Pro Ser Thr Pro Arg Ala Thr Thr Leu Thr Pro Ala
340 345 350

Pro Ala Thr Thr Val Thr Arg Ser Thr Ser Arg Ala Gly Asn Arg Cys
355 360 365

Cys Lys Thr Tyr Asp His His Trp Leu Ser His His Ala Glu Ala Leu
370 375 380

Asp Pro Leu Thr Leu Pro Thr Gly Pro Leu Gln Pro Leu Arg Val Ile
385 390 395 400

Thr Ala Arg Arg Pro Ser Val Ser Arg Glu Ser Leu Pro Ser Ile Pro
405 410 415

Gly Arg Ile Ser Thr Gly Arg Gly His Arg Gln Pro Gly Gly Pro Ala

420 425 430

Arg Pro Thr Ser Leu Glu Ser Phe Thr Asn Ala Pro Pro Thr Thr Ile
435 440 445

Ser Glu Pro Ser Thr Arg Ala Ala Gly Pro Gly Arg Phe Arg Asp Asn
450 455 460

Arg Met Asp Arg Arg Glu His Gly His Arg Asp Pro Asn Val Val Pro
465 470 475 480

Gly Pro Pro Lys Pro Ala Lys Glu Lys Pro Pro Lys Lys Lys Ala Gln
485 490 495

Asp Lys Ile Leu Ser Asn Glu Tyr Glu Glu Lys Tyr Asp Leu Ser Arg
500 505 510

Pro Thr Ala Ser Gln Leu Glu Asp Glu Leu Gln Val Gly Asn Val Pro
515 520 525

Leu Lys Lys Ala Lys Glu Ser Lys Lys His Glu Lys Leu Glu Lys Pro
530 535 540

Glu Lys Glu Lys Lys Lys Lys Lys Lys Lys
545 550

<210> 576
<211> 23
<212> PRT
<213> Homo sapiens

<400> 576
Met Leu Ala Leu Leu Gly Leu Leu Ala Gly Thr Glu His Pro Pro Gly
1 5 10 15

Pro Gln Gly Pro Gly Pro Ser
20

<210> 577
<211> 25
<212> PRT
<213> Homo sapiens

<400> 577
Met Val Asn Ile Phe Gly Phe Val Ser Cys Ile Val Phe Val Val Ala
1 5 10 15

Val Gln Leu Cys Tyr Met Lys Gln Pro
20 25

<210> 578
<211> 122
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (92)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (100)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (109)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (116)
<223> Xaa equals any amino acid

<400> 578
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Met Leu Ala Leu Thr Leu Ala Lys Ala Asp Ser Pro Arg Thr Ala Leu
  1               5                  10                  15

Leu Cys Ser Ala Trp Leu Leu Thr Ala Ser Phe Ser Ala Gln Gln His
             20                  25                  30

Lys Gly Ser Leu Gln Val His Gln Thr Leu Ser Val Glu Met Asp Gln
         35                  40                  45

Val Leu Lys Ala Leu Ser Phe Pro Lys Lys Lys Ala Ala Leu Leu Ser
     50                  55                  60

Thr Ala Ile Leu Cys Phe Leu Arg Thr Ala Leu Arg Gln Ser Phe Ser
 65                  70                  75                  80

Ser Ala Trp Asn Pro Gly Ala Leu Lys Gly Pro Xaa Thr Ala Ala Thr
                 85                  90                  95

Lys Asp Thr Xaa Leu Thr Ser Leu Arg Met Ser Lys Xaa Gly Pro Gly
            100                 105                 110

His Trp Ala Xaa Lys Thr Ser Trp Cys Lys
        115                 120
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<210> 579
<211> 216
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (6)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (18)
<223> Xaa equals any amino acid

<400> 579
Cys Phe Pro Trp Gly Xaa Ala Leu Arg Gln Lys Leu Phe Pro Ser Ala
1   5   10   15

Leu Xaa Ala Leu Val Pro Ser Gly Ala Gln Pro Leu Pro Ala Thr Lys
            20   25   30

Asp Thr Val Leu Ala Pro Leu Arg Met Ser Gln Val Arg Ser Leu Val
        35   40   45

Ile Gly Leu Gln Asn Leu Leu Val Gln Lys Asp Pro Leu Leu Ser Gln
    50   55   60

Ala Cys Val Gly Cys Leu Glu Ala Leu Leu Asp Tyr Leu Asp Ala Arg
65   70   75   80

Ser Pro Asp Ile Ala Leu His Val Ala Ser Gln Pro Trp Asn Arg Phe
                85   90   95

Leu Leu Phe Thr Leu Leu Asp Ala Gly Glu Asn Ser Phe Leu Arg Pro
            100   105   110

Glu Ile Leu Arg Leu Met Thr Leu Phe Met Arg Tyr Arg Ser Ser Ser
        115   120   125

Val Leu Ser His Glu Glu Val Gly Asp Val Leu Gln Gly Val Ala Leu
    130   135   140

Ala Asp Leu Ser Thr Leu Ser Asn Thr Thr Leu Gln Ala Leu His Gly
145   150   155   160

Phe Phe Gln Gln Leu Gln Ser Met Gly His Leu Ala Asp His Ser Met
                165   170   175

Ala Gln Thr Leu Gln Ala Ser Leu Glu Gly Leu Pro Pro Ser Thr Ser
            180   185   190

Ser Gly Gln Pro Pro Leu Gln Asp Met Leu Cys Leu Gly Gly Val Ala
        195   200   205

Val Ser Leu Ser His Ile Arg Asn
    210   215

<210> 580
<211> 127
<212> PRT
<213> Homo sapiens

<400> 580
Met Leu Pro Leu Leu Ile Ile Cys Leu Leu Pro Ala Ile Glu Gly Lys
1   5   10   15

Asn Cys Leu Arg Cys Trp Pro Glu Leu Ser Ala Leu Ile Asp Tyr Asp
            20   25   30

Leu Gln Ile Leu Trp Val Thr Pro Gly Pro Pro Thr Glu Leu Ser Gln
        35   40   45

Ser Ile His Ser Leu Phe Leu Glu Asp Asn Asn Phe Leu Lys Pro Trp
50 55 60

Tyr Leu Asp Arg Asp His Leu Glu Glu Glu Thr Ala Lys Phe Phe Thr
65 70 75 80

Gln Val His Gln Ala Ile Lys Thr Leu Arg Asp Asp Lys Thr Val Leu
85 90 95

Leu Glu Glu Ile Tyr Thr His Lys Asn Leu Phe Thr Glu Arg Leu Asn
100 105 110

Lys Ile Ser Asp Gly Leu Lys Glu Lys Glu Pro His Pro Ser Pro
115 120 125

<210> 581
<211> 164
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (126)
<223> Xaa equals any amino acid

<400> 581
Met Leu Pro Leu Leu Ile Ile Cys Leu Leu Pro Ala Ile Glu Gly Lys
1 5 10 15

Asn Cys Leu Arg Cys Trp Pro Glu Leu Ser Ala Leu Ile Asp Tyr Asp
20 25 30

Leu Gln Ile Leu Trp Val Thr Pro Gly Pro Pro Thr Glu Leu Ser Gln
35 40 45

Ser Ile His Ser Leu Phe Leu Glu Asp Asn Asn Phe Leu Lys Pro Trp
50 55 60

Tyr Leu Asp Arg Asp His Leu Glu Glu Glu Thr Ala Lys Phe Phe Thr
65 70 75 80

Gln Val His Gln Ala Ile Lys Thr Leu Arg Asp Asp Lys Thr Val Leu
85 90 95

Leu Glu Glu Ile Tyr Thr His Lys Asn Leu Phe Thr Glu Arg Leu Asn
100 105 110

Lys Ile Ser Asp Gly Leu Lys Glu Lys Gly Ala Pro Pro Xaa Ser Met
115 120 125

Asn Ala Phe Pro Ala Pro Ser Pro Thr Cys Thr Pro Glu Pro Leu Gly
130 135 140

Ser Val Cys Leu Pro Ser Thr Ser Val Ser Leu Pro Ser His Leu Pro
145 150 155 160

Gly Ser Leu Gln

<210> 582
<211> 71
<212> PRT
<213> Homo sapiens

<400> 582
Met Val Gln Gly Pro Leu Thr His Leu Met Leu Val Leu Leu Ile Ser
1 5 10 15

Leu Ile Phe Leu Ser Arg Gly Ser Gly Arg Ala Trp Ala Phe Ser His
20 25 30

Ser Cys Phe Lys Thr Ser Asp Leu Leu Pro Cys Arg Asn Arg Trp Glu
35 40 45

Val Ile Glu Phe Leu His Tyr Ser Asn Leu His Ser His Ile Ser Leu
50 55 60

Ser Val Thr Lys Thr Phe Leu
65 70

<210> 583
<211> 140
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (136)
<223> Xaa equals any amino acid

<400> 583
Met Ala Ser Leu Gly Leu Gln Leu Val Gly Tyr Ile Leu Gly Leu Leu
1 5 10 15

Gly Leu Leu Gly Thr Leu Val Ala Met Leu Leu Pro Ser Trp Lys Thr
20 25 30

Ser Ser Tyr Val Gly Ala Ser Ile Val Thr Ala Val Gly Phe Ser Lys
35 40 45

Gly Leu Trp Met Glu Cys Ala Thr His Ser Thr Gly Ile Thr Gln Cys
50 55 60

Asp Ile Tyr Ser Thr Leu Leu Gly Leu Pro Ala Asp Ile Gln Ala Ala
65 70 75 80

Gln Ala Met Met Val Thr Ser Ser Ala Ile Ser Ser Leu Ala Cys Ile
85 90 95

Ile Ser Val Val Gly Met Arg Cys Thr Val Phe Cys Gln Glu Ser Arg
100 105 110

Ala Lys Asp Arg Val Ala Val Ala Gly Gly Val Phe Phe Ile Leu Gly
115 120 125

Ser Leu Leu Gly Phe Ile Pro Xaa Ala Trp Asn Leu

130 135 140

<210> 584
<211> 86
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (33)
<223> Xaa equals any amino acid

<220>
<221> SITE
<222> (43)
<223> Xaa equals any amino acid

<400> 584
Arg Arg Phe Tyr Ser Pro Leu Val Pro Asp Ser Met Lys Phe Glu Ile
1 5 10 15

Gly Glu Ala Leu Tyr Leu Gly Ile Ile Ser Ser Leu Phe Ser Leu Ile
20 25 30

Xaa Gly Ile Ile Leu Cys Phe Ser Cys Ser Xaa Gln Arg Asn Arg Ser
35 40 45

Asn Tyr Tyr Asp Ala Tyr Gln Ala Gln Pro Leu Ala Thr Arg Ser Ser
50 55 60

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<211> 3029
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (4)..(4)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (150)..(150)
<223> n equals a,t,g, or c

<400> 625
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<210> 626
<211> 224
<212> DNA
<213> Homo sapiens

<400> 626

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ggtggaggtt gcagtgagct gagatcatgc cactgcactc cagcctgggt gacagagcga   180
gactctctct ccaaaaaaaa aaaaaaaaac ctagaccaga tgca                    224
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<210> 627
<211> 468
<212> DNA
<213> Homo sapiens

<400> 627

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attgcagagc tgcaagagaa ttctgagatc aacaggtctt tttccttcat ttaccagctg   180
agaaacttgg ggtcatagga gattaagatt gtttatctta ccagttgaat tcaatacttt   240
cagaaataat tgttagaatt cagtgaaagt tattctctta aaagtacact gcttttcagc   300
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tctgggaaag gctgtcaaat gtttattcta gaatccagca actcccagat gtccatctcc   420
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<210> 628
<211> 222
<212> DNA
<213> Homo sapiens

<400> 628

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tggaggttgc agtgagctga gatcatgcca ctgcactcca gcctgggtga cagagcgaga   180
ctctctctcc aaaaaaaaaa aaaaaaacct agaccagatg ca                      222
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<210> 629

<211> 468
<212> DNA
<213> Homo sapiens

<400> 629
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<210> 630
<211> 224
<212> DNA
<213> Homo sapiens

<400> 630
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gactctctct ccaaaaaaaa aaaaaaaaac ctagaccaga tgca 224

<210> 631
<211> 1854
<212> DNA
<213> Homo sapiens

<400> 631
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<210> 632
<211> 2128
<212> DNA
<213> Homo sapiens

<400> 632
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<210> 633
<211> 2129
<212> DNA
<213> Homo sapiens

<400> 633
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<211> 290
<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/08276

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/00; C07K 1/00

US CL : 514/12; 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/12; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,858,716 A (ELSHOURBAGY et al.) 12 January 1999 (12.01.1999), SEQ ID NO: 2, amino acids 438-644, columns 25-30.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 July 2002 (15.07.2002)

Date of mailing of the international search report

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Name and mailing address of the ISA/US

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT	International application No. PCT/US02/08276

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: Claims 1-4 in part, as they relate to SEQ ID NO: 300

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Note that Claims 1-12, 15, and 18, which begin with the words "Use of ..." have been treated as method claims with the phrase "A method of using" substituted for "Use of."

Groups 1-289, Claims 1-4 in part, drawn to a method of using a polypeptide for the preparation of a diagnostic or pharmaceutical composition, each group defined by a unique amino acid sequence selected from SEQ ID NO: 300-588.

Groups 290-578, Claims 5 and 6 in part, drawn to a method of using an antibody or a fragment thereof for the preparation of a diagnostic or pharmaceutical composition, each group defined by the specificity of the antibody used.

Groups 579-877, Claims 7-10 in part, drawn to a method of using a nucleic acid molecule for the preparation of a diagnostic or pharmaceutical composition, each group defined by a unique nucleotide sequence selected from SEQ ID NO: 1-299.

Groups 878-1166, Claims 11-12 in part, drawn to a method of using an agonist or antagonist for the preparation of a diagnostic or pharmaceutical composition, each group defined by the polypeptide bound by the agonist or antagonist.

Groups 1167-1455, Claims 13, 14, 16, and 17 in part, drawn to a polypeptide, each group defined by a polypeptide sequence selected from SEQ ID NO: 300-588.

Group 1456-1744, Claims 15 and 18 in part, drawn to a method of using a polypeptide for identifying binding partners, each group defined by the sequence of the polypeptide used.

Groups 1745-2033, Claims 19 and 20 in part, drawn to an antibody that binds a polypeptide comprising a sequence selected from SEQ ID NO: 300-588, each group defined by the specificity of the antibody.

Groups 2034-2332, Claims 21-32 in part, drawn to a nucleic acid molecule, each group defined by a nucleotide sequence selected from SEQ ID NO: 1-299. The first claimed invention, groups 1-289, lack unity because they represent a method of using plurality of polypeptides as diagnostic or pharmaceutical compositions. The polypeptides, identified as SEQ ID NO: 300-588, each have a different sequence. Because the sequence, structure, and function of each polypeptide is unique, the claimed inventions do not share a common special technical feature and unity is therefore lacking. Each individual polypeptide sequence is considered to constitute a special technical feature.

Groups 290-578 represent methods of using an antibody for the preparation of a diagnostic preparation wherein the antibody binds an amino acid sequence selected from SEQ ID NO: 300-588. The amino acid sequences SEQ ID NO: 300-588 lack unity as described above. Each antibody of groups 290-578 bind specifically to one of the polypeptides of SEQ ID NO: 300-588. The differences in protein affinity among the antibodies is based on differences in the structure among the antibodies and results in molecules with different functions. As a result, the antibodies do not share a common special technical feature. Because each method relies on a unique antibody, the methods will differ in their results and applications. Therefore unity among the methods is deemed lacking.

Although the antibodies of groups 290-578 bind specifically to the polypeptides of SEQ ID NO: 300-588, the antibodies are different from the polypeptides in their structure, sequence, and function, and therefore lack unity with the polypeptides.

Groups 579-877 represent methods of using a nucleic acid molecule for the preparation of a diagnostic composition wherein the nucleic acid is selected from SEQ ID NO: 1-299. Because the sequence, structure, and function of each polynucleotide is unique, the polynucleotides do not share a common special technical feature. Because each method relies on a unique polynucleotide, the methods will differ in their results and applications. Therefore unity among the methods is deemed lacking.

Groups 878-1166 represent methods of using an agonist or antagonist for the preparation of a diagnostic composition wherein the agonist or antagonist binds to a polypeptide of SEQ ID NO: 300-588. The polypeptides of SEQ ID NO: 300-588 lack unity as described above. Because each method depends on the ability of an agonist or antagonist to bind to a unique protein, and because the protein targets differ in their structure and function, the results produced by each of the methods will differ. Therefore unity among the methods is deemed lacking.

Groups 1167-1455 represent polypeptides of SEQ ID NO: 300-588. The polypeptides lack unity as described above.

Groups 1456-1744 represent methods of using a polypeptide of SEQ ID NO: 300-588 to identify binding partners for the polypeptide. The polypeptides of SEQ ID NO: 300-588 lack unity as described above. Because each method depends on a unique polypeptide sequence, the binding partners identified by each method will differ. Therefore unity among the methods is deemed lacking.

Groups 1745-2033 represent antibodies which bind specifically to polypeptides of SEQ ID NO: 300-588. These antibodies lack unity as described above.

Groups 2034-2332 represent nucleic acid molecules of SEQ ID NO: 1-299. The nucleic acid molecules lack unity as described above.

Continuation of B. FIELDS SEARCHED Item 3:
US Patent Database; SwissProt, PIR,
search for SEQ ID NO: 300